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Family Medicine

Principles and Practice

Eighth Edition

Springer

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Paul M. Paulman • Robert B. Taylor •
Audrey A. Paulman • Laeth S. Nasir
Editors

Family Medicine

Principles and Practice

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With 198 figures and 357 Tables

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“Thanks to all family physicians and others who provide primary care to their patients; without you, there would be no reason to publish this book.”

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Preface to the Eighth Edition

Family Medicine: Principles and Practice, eighth edition, is designed to provide point of care and reference information for family physicians, mid-level providers, residents, medical and osteopathic students, and all others who provide primary care for patients. The supervising editors from the seventh edition also supervised the production of this volume. The fact that only a few chapters were removed and a few chapters added is yet another tribute to Dr. Robert Taylor's book design as he published the first of this series and continues to serve on the editorial team and provide advice and counsel. Given that this project took place during the COVID-19 pandemic, the addition of a chapter covering pandemics is very timely.

The editors are very grateful to the staff and administrators at Springer and chapter authors who not only provided very good chapter manuscripts but also cared for themselves and their families during this pandemic. My personal thanks to Dr. Audrey Paulman and Dr. Laeth Nasir for their great work on the editorial team, and of course, thank you to all our readers/users of this book, as I said in the preface of the previous edition: providing good information which helps our readers improve the care of their patients will be our highest marker of success.

Stay well.
For the editors,
Omaha, USA
December 2021

Paul M. Paulman
Lead Editor

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Preface to the First Edition

As we celebrate the publication of the 8th edition of Taylor's Family Medicine: Principles and Practice, we are also celebrating the 45th anniversary of the publication of the landmark textbook Taylor's Family Medicine: Principles and Practice, 1st edition.

This book is about people: the patient, the family, and the family physician. It presents health problems of the patient and health care by the physician in the context of mankind's most enduring societal unit – the family.

The objectives in preparation of this book have been:

1. To compile in a single textbook the fundamental principles of family medicine and the methods to implement these principles on a global basis.
2. To describe the approach of the family physician to clinical problems.
3. To help identify the clinical content of family medicine.
4. To provide a data base which can serve as a day-by-day reference source for the resident physician and clinician.
5. To explore the history and philosophy of the family practice movement.

These objectives were pursued by seeking the advice and participation of family medicine educators and practitioners around the world; preparing a book format intended to present data in a logical, cohesive manner; selecting authors based on their interests and contributions in family medicine; considering the priorities family physicians ascribe to achieving competence in various clinical areas; and including chapters telling the evolution of the modern family physician and his focus on the patient in relation to the family.

A new textbook should differ significantly from other literature in the field. The following 94 chapters represent new material prepared specifically for this first edition, including many facts and theories never before in print. There are several chapters giving personal viewpoints on topics pertinent to the specialty. The format employs units of sequential chapters that allow full elucidation of concepts. The broad scope of family medicine is covered, including sections on family medicine education, behavior and counseling, and the full spectrum of clinical medicine. The development of clinical chapters has included the Competence Priority Classification of Behavior, Concepts, and Skills in Family Medicine, a unifying taxonomy that is intended to be academically instructive and clinically relevant.

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The editor expresses appreciation to the 128 contributing authors and to the four associate editors: John L. Buckingham, E. P. Donatelle, William E. Jacott, and Melville G. Rosen. Also gratefully acknowledged is the cooperation of the American Academy of Family Physicians, The American Board of Family Practice, the College of Family Physicians of Canada, and the Society of Teachers of Family Medicine. My family – Anita, Diana, and Sharon – shared in the preparation of this book, as did literally hundreds of other persons too numerous to list individually, and to whom the editors, authors, and readers are indebted.

R.B.T

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Acknowledgments

We dedicate this book to all the workers who labored to keep us healthy, fed, and safe during the COVID-19 pandemic. There will never be adequate recognition or rewards for these incredible men and women; nevertheless, we'd like to add our thanks.

We have many more people to thank: Dr. Robert Taylor has continued to inspire us in his role as founder of this series of reference books; his advice and counsel have been invaluable.

Saskia Ellis, our production manager, provided a steady, consistent guiding hand throughout the production process. When it seemed that we had reached insurmountable roadblocks, Saskia was there to let us know how much progress we had made and how we weren't THAT far behind schedule. We appreciate your work, Saskia!

Sylvia Blago has also been inspirational for us and has helped us keep our eye on the prize. Having worked with Sylvia on previous projects, we have had great production experiences and she did not disappoint during this project. Thank you, Sylvia.

Our chapter authors came through with great material, while also caring for their patients and keeping themselves and their families safe from the virus. We are in your debt.

Personal thanks to Dr. Audrey Paulman and Dr. Laeth Nasir, volume editors, for their great efforts to recruit chapter authors and overcome any and all problems in order to bring this book to publication. We look forward to future editions of this reference book from Dr. Laeth Nasir and his team. Future editions of this book will be outstanding.

For the editors,
Paul M. Paulman
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Abbreviations

ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase (SGPT)
ANA	Antinuclear antibody
AST	Aspartate aminotransferase (SGOT)
bid	Twice a day
BP	Blood pressure
bpm	Beats per minute
BS	Blood sugar
BUN	Blood urea nitrogen
CBC	Complete blood count
CHF	Congestive heart failure
Cl^-	Chloride
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CSF	Cerebrospinal fluid
CT	Computed tomography
cu mm	Cubic millimeter
CXR	Chest X-ray
d	Day, daily
dL	Deciliter
DM	Diabetes mellitus
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
FDA	United States Food and Drug Administration
FM	Family medicine
FP	Family physician
g	Gram
GI	Gastrointestinal
Hb	Hemoglobin
Hg	Mercury
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
hr	Hour

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hs	Hour of sleep, at bedtime
HTN	Hypertension
IM	Intramuscular
INR	International normalized ratio
IU	International unit
IV	Intravenous
K^+	Potassium
kg	Kilogram
L	Liter
LD or LDH	Lactate dehydrogenase
mEq	Milliequivalent
μg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mm^3	Cubic millimeter
MRI	Magnetic resonance imaging
Na^+	Sodium
NSAID	Nonsteroidal anti-inflammatory drug
po	By mouth (per os)
PT	Prothrombin time
PTT	Partial thromboplastin time
q	Every
qd	Every day, daily
qid	Four times a day
qod	Every other day
RBC	Red blood cell
SC	Subcutaneous
sec	Second
SGOT	See AST
SGPT	See ALT
STD	Sexually transmitted disease
TB	Tuberculosis
tid	Three times a day
TSH	Thyroid stimulating hormone
U	Unit
UA	Urine analysis
WBC	White blood cell, white blood count
WHO	World Health Organization

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Part I

The Principles of Family Medicine

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Family Medicine: Fifty Years of Caring for America

1

John W. Saultz, Robert B. Taylor, and Paul M. Paulman

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In its early years, the specialty of family medicine had originated within the lifetimes of its practitioners. As family medicine celebrates its 50th anniversary, the founding generation has retired, and today's family physicians (FPs) are providing care in a very different world. Few are in solo practice. Many are employed in integrated health systems. and most use electronic information systems to document care and communicate with patients. Since its beginning in 1969, family medicine has become one of medicine's largest and most successful specialties. And yet many of its current members are unfamiliar with the inspiring story of how the specialty began. For this reason, this book begins with an overview of the specialty's origin, evolution, and current status. The goal of this chapter is not simply to preserve a record of the past but also to explain how family medicine came to be the way it is, to delineate lessons learned by its first two generations of leaders, and to provide a context for building the discipline's future.

A Short History of the Specialty

Family medicine in the United States evolved from general practice, which was the dominant force in health care until the mid-twentieth century. The story of how this happened can be told in at least three ways, and each of these creation stories offers insight into the specialty's traditions and values.

Family Medicine as a Social Movement

Family practice arose as a specialty during the 1960s – the time of the Vietnam War, the civil rights movement, and widespread social unrest – a time not unlike today when the wisdom of experts was being challenged. Rapid population growth and accelerating medical specialization following World War II precipitated a decline in access to primary health care at the community level in the United States. Although a handful of general practice residencies were established in the 1950s, generalist training was inadequate in both quality and capacity. In response, the American public and farsighted health policy planners decried the fragmentation of American medicine and called for the creation of a physician who specialized in primary health care. Three influential reports, all published in 1966, made the case for what eventually became family medicine. These reports have historically been referred to by the names of their chairmen: the Folsom report, the Millis report, and the Willard report.

The Folsom report was a report of a national commission on community health services and was sponsored by the American Public Health Association and the National Health Council [1]. This commission's 4-year investigation produced 14 recommendations. The most pertinent to the evolving specialty of family practice was a task force report entitled *The Changing Role of the Personal Physician*, which concluded that all Americans should have "personal physicians" to ensure the integration and continuity of their medical services. The report emphasized the importance of preventive medicine, the use of community resources, and the importance of caring for the patient in a continuity context.

The second report was from the Citizens' Commission on Graduate Medical Education, which was sponsored by the American Medical Association [2]. This commission focused on graduate medical education. Specifically, it suggested that "primary physicians" be trained to replace the dwindling number of general practitioners. The Millis report specifically addressed the importance of comprehensive clinical skills, continuity of care,

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coordination of services, and preventive services to be provided by these new primary physicians.

The third report was from the Committee on Education for Family Practice, which was sponsored by the Council on Medical Education of the American Medical Association (AMA) and was charged to review AMA policy regarding the future of general practice [3]. The Willard report specifically called for a new kind of specialist in family practice and even specified the outline of a training program for "family physicians." It also recommended the establishment of a certifying board in family practice. Dr. Willard was the dean of medicine at the University of Kentucky. At that time, the chairman of the department of medicine at that medical school was Edmund Pellegrino. Because of his experience with general practice residents in the 1950s, Dr. Pellegrino chose to appoint two general practitioners to the full-time faculty in the department of medicine [4]. One of these individuals – Nicholas J. Pisacano – was an idealistic and scholarly general practitioner who was already one of the most outspoken advocates for certification in the field. When the American Board of Family Practice ultimately achieved recognition as a certified specialty board, it was Dr. Pisacano who became its founding executive director.

With the support of the American Academy of General Practice (AAGP) and US general practitioners, family practice became the 20th American medical specialty in 1969. The story of these three influential reports provides the first of family medicine's creation stories – a story focused on needs identified by public policy-makers during a time of social unrest and reform.

Family Medicine as a Defense of General Practice

Family medicine also arose as a political and professional defense of the general practitioner. Leaders in the American Academy of General Practice (AAGP) were alarmed as early as the 1940s by the declining number of medical students choosing to enter general practice [5]. Declining numbers threatened the ability of general practitioners to obtain and retain hospital privileges and undermined their prestige and political influence within the profession. While the first creation story is fundamentally a story of social activism, there is also a side of the story that was about preserving a way of life for those practicing in community.

Four early decisions helped shape the future of the new specialty, and all were about enhancing the quality and prestige of the field. A *specialty certifying board* – the American Board of Family Practice – was created in 1969. *Three-year residency training programs* were established in contrast to the prior norm of a single year of internship for general practitioners. *Mandatory recertification* was pioneered by the ABFP, and all US board-certified family physicians still must undergo periodic recertification. Most other specialties have since established similar requirements. Finally, *mandatory continuing medical education* was required by both the American Academy of Family Physicians (AAFP) and the American Board of Family Practice.

The new specialty began with 15 residency training programs, most converted from the few existing general practice programs. Federal grant programs supported new departments of family medicine in medical schools, and clinical departments of family practice were formed in community hospitals across America. From 1969 until today, the family medicine movement has continued to gain momentum, with solid gains in student recruitment, more residents in training, increased numbers of board-certified FPs in practice, and family physicians in leadership positions in clinical medicine and academia.

Family Medicine as a Reform Movement Within Medicine

The birth of family practice can also be viewed as an intellectual and philosophical reform of medicine as a profession. The new specialty faced extensive opposition from both organized medicine and from the academic world of the medical schools. This criticism was usually based on the argument that there was no unique

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field of knowledge constituting family practice. Instead, the knowledge, skills, and attitudes of a family physician were felt to be derived from the fields of surgery, obstetrics and gynecology, pediatrics, and so on. The early residencies were largely dependent on educational rotations with each of these specialties, and this no doubt gave credence to this claim. Since medical school departments generally reflect an academic discipline instead of a practice specialty, the perceived lack of an intellectual foundation to the field severely hampered the establishment of departments of family medicine in medical schools. Departments were established most quickly in publicly funded institutions, where political pressure from state legislatures was brought to bear to effect these changes. A few private universities continue to hold out to this day.

But there was a much more fundamental reason for the opposition. After the Flexner report of 1910, American medicine had evolved into a biologic science focused on better understanding the mechanisms by which diseases arise and are treated. On the one hand, this model can be credited with astonishing advances in medical science and resulting improvements in the length and quality of life over the twentieth century. But this model was also directly responsible for a loss of patient-centeredness in favor of a disease-oriented approach to care [6]. From its very beginning, family medicine was a counterculture movement pushing back on these trends – and counterculture movements threaten the status quo. A series of essays entitled *The Intellectual Basis of Family Practice* was published by G. Gayle Stephens during family medicine's first decade [7]. Stephens' work became a rallying call for many of the first generation of family medicine residents. Family medicine has certainly been a social movement about making care available to the American people, and its founding generation of physicians was certainly interested in preserving and improving general practice. But many others entered the field to change American medicine intellectually by incorporating social, behavioral, and population scientific methods into a world dominated by biology and reductionism.

The Evolution of Family Medicine

At its birth, the specialty's name was *family practice* in large measure as a tribute to its roots in general practice. The term *family medicine* was used to refer to the academic discipline as something separate from the clinical specialty. Family physicians in the 1970s still largely practiced in solo practices and small groups with one another. Most were self-employed small business owners, and the care was delivered in one-on-one relationships between the doctor and patient. By the 1980s, a growing number of family physicians were in group practices; solo practice was becoming rare as the administrative complexities of medicine made economies of scale and shared administrative resources more efficient. The 1980s also brought increasing scrutiny to the high cost of medical care and insurance companies evolved from simply paying claims to mounting efforts to manage care. This inevitably resulted in attempts to limit specialty referrals, emergency department visits, and hospitalizations and the responsibility to manage cost often fell to those practicing primary care. The 1990s witnessed a substantial increase in medical student interest in family medicine and, for a while, it seemed that the imbalance between primary and specialty care was being corrected. Family physicians even began to play important roles in the management of health plans and medical groups.

Unfortunately, these gains were short lived. By the early 2000s, it became clear that the administrative complexity of the managed care era had failed to adequately control health-care inflation. The insurance system moved away from structures based on primary care utilization management and began passing increasing costs to patients as out-of-pocket deductibles and copayments. Primary care again fell in prestige and student interest declined. In 2002, the specialty of family medicine conducted a strategic planning process call the *Future of Family Medicine* project (FFM) [8]. The outcome of this process was documented in six reports, all published in the discipline's new research journal the *Annals of Family Medicine* in 2004. One recommendation from this process was that the

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specialty name should change from family practice to family medicine and organizations like the American Board of Family Medicine changed their names accordingly. The most important recommendations of the FFM all related to a proposed new model of clinical care that eventually came to be known as the patient-centered medical home (PCMH) [9]. At its heart, the PCMH called for an evolution from the one-on-one doctor patient relationship to a notion of team-based care in which family medicine practices were asked to create and empower teams of providers to share responsibility for their patients. Systems were devised to certify practices as PCMHs and, by the end of the decade, electronic information and communication systems became requirements for PCMH designation. Although some of the initial cost of these electronic health records was supported by the federal government, their ongoing cost led to practice expenses that could not easily be borne by the revenues generated from primary care practice alone. This further catalyzed consolidation of practices into larger and larger groups and, in many cases, to practice networks owned and supported by hospital-based systems.

Following the great recession of 2008, cost containment efforts had again failed to limit continuing increases in health-care spending and large delivery systems managed to increase revenues even as the overall economy lagged. But as cost pressure increased on these systems, the need for larger and more effective primary care systems became apparent. While large delivery systems supported growth in primary care, they generally opposed increasing reimbursement for these services, preferring instead to move hospital and specialty profits into primary care investments. Under such conditions, more and more family physicians became employees of large health systems and medicine evolved from loosely linked small businesses to influential and sometimes monopolistic corporate entities.

As the decade of the 2010s ends, family medicine again stands at crossroads. On the one hand, its values remain rooted in the one-on-one doctor-patient relationship with personal accountability resting on the physician. But the discipline has also embraced the need for improvements in population outcomes as measured by electronic health data, with accountability lying with practice organizations. In 2014, another specialty-wide strategic planning effort was undertaken. This project, called *Family Medicine for America's Health*, eventually recommended an expansion of the PCMH model to fully integrate mental health and population health into the primary care system [10]. Today, practices throughout the country are struggling to make these recommendations a reality. But this enhanced PCMH model adds even more costs to the primary care system, and it remains to be seen if reimbursement reform will support such systems in the long term.

Throughout its history, family medicine has struggled to attract a sufficient number of new family physicians even as more and more responsibility has fallen to the primary care system. By 2020, the number of medical schools and the number of graduating medical students have grown substantially, but family medicine still struggles with the inescapable reality that there are not enough family physicians to care for the American people. So a gap widens between family medicine ideals and the pressing realities of family physicians' day to day work.

In 1987 Pellegrino [11] commented: "The birth of Family Practice two decades ago, and its development as a genuine specialty within the bodies of both medical practice and academia is surely one of the most remarkable stories in contemporary medical history." Now 50 years old, the specialty remains one of the shining accomplishments of twentieth-century medicine. Family medicine was born in an era of social change to protect and professionalize general practice and to reform American medicine. The need for the discipline has never been more apparent than it is today.

Family Medicine in the United States in 2020

In 2018, there were 985,000 licensed physicians in the United States [12] of which 139,000 were professionally active FPs [13]. There are 131,000 members of the AAFP [14] and 92,000

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diplomates certified by the ABFM [15]. The specialty had 679 accredited residency programs with 13,924 residents in training during the 2019–2020 academic years making it the largest specialty in terms of programs and the second largest in terms of resident enrollment [16]. Family medicine is well-established in nearly all of the nation's medical schools, and there are required courses and established research programs throughout the country. In 2015, 6738 faculty members in 134 academic departments of family medicine published 3002 peer-reviewed scientific papers and federal research funding supported over half of this work [17].

The specialty has been undeniably successful as measured by these accomplishments. And yet there are concerning trends. Most of what is known about the clinical work of family physicians is based on studies of ABFM diplomates, admittedly a subset of all family physicians. But evidence from the ABFM suggests steep declines in the number of family physicians delivering maternity care, caring for hospitalized patients, and caring for children, and these changes have begun to impact the availability of basic health services, particularly in rural and under-served communities that are most likely to be served by family physicians [18]. Burnout and career dissatisfaction are major problems among physicians overall, and studies estimate that over half of the nation's family physicians describe themselves as burned out. Although there has been rapid growth in the number of residency programs, family medicine attracted only 12.6% of US allopathic and osteopathic medical school seniors in 2018 [19]. Even more concerning, striking racial and geographic disparities in health status have widened even though more Americans than ever have health insurance coverage. As proud as family physicians justifiably are, the true promise of family medicine remains unachieved in America.

Family Medicine and General Practice Around the World

The international group uniting family medicine and general practice is the World Organization of National Colleges, Academies, and Academic Associations of General Practitioners/Family Physicians (WONCA). More commonly known as the World Organization of Family Doctors, WONCA is comprised of 118 member organizations in 131 countries, with membership of about 500,000 family doctors worldwide [20]. WONCA advocates for family medicine internationally and hosts regional meetings in seven regions around the world. Some countries have retained the title general practitioner while others have adopted the name family physician, but around the world, the core principles of the discipline are pretty much the same. Much of WONCA's international work has referenced the Alma-Ata Declaration of 1978 which was adopted by the World Health Organization and defines the international importance of primary care. Alma-Ata stands as one of the most important statements of public health principle of the twentieth century, and this work has catalyzed the development of family medicine in most of the countries in the world with special emphasis on developing countries.

The nature of day-by-day practice in family medicine varies from country to country. In some areas, such as the United States and Canada, family physicians often have an active role in hospital care. In other settings, such as in the United Kingdom and Latin America, family medicine is chiefly office-based, often supplemented by home care. But family physician and general practitioners around the globe deliver care based on shared academic principles.

Academic Principles of Family Medicine

The official definition of family medicine is:

> Family medicine is the medical specialty which provides continuing, comprehensive health care for the individual and family. It is a specialty in breadth that integrates the biological, clinical and behavioral sciences. The scope of family medicine encompasses all ages, both sexes, each organ system and every disease entity. [21]

This definition focuses on family medicine as a specialty of medicine and not on family medicine

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as an academic discipline. From the specialty's early days, some authors have considered *family medicine* to be the name of the academic discipline on which the specialty is based and have discriminated between an academic discipline and a medical specialty. Now that the specialty name is also *family medicine*, the distinction might be a moot point. Nevertheless, the specialty's 50-year history has produced a body of scholarly work that is uncontestably unique and important, and this body of work represents an academically rigorous intellectual field. Although this chapter will not attempt to list them all (in fear of offending by omission), there are currently at least 20 English language family medicine journals worldwide as well as hundreds of books and thousands of scholarly publications in clinical and health policy journals [22]. So, while the earliest scholarship in the field was focused on describing what family physicians do, the field has now broadened to the study of how practice outcomes can be optimized. Although there continues to be considerable debate about the precise definition and content of family medicine as an area of study, family medicine as an academic field is best defined as *the study of how best to deliver efficient and affordable primary care to populations and communities* [23].

Primary care is a term derived from the public health literature and refers to first-contact health services delivered at the community level, in contrast to secondary care (care delivered by specialty consultants and in community hospitals) and tertiary care (care delivered in specialized academic settings). The most uniformly accepted definition of primary care was published after extensive study by the National Academy of Sciences Institute of Medicine in 1996:

> Primary care is the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community. [24]

Nearly all family physicians provide primary care, but historically they have also provided services such as maternity and hospital care that would be characterized as secondary care. Furthermore, while other physician groups (general internal medicine and general pediatrics) and other professionals (nurse practitioners and physician assistants) deliver primary care, the study of how primary care is optimized has largely become the domain of scholars in family medicine. Importantly, the term "scholars of family medicine" is not limited to family physicians. Departments of family medicine now contain faculty members with backgrounds in over a dozen fields including the social and behavioral sciences, health economics, public health, statistics, nursing, and communications in addition to medicine.

The scholarly development of family medicine is exemplified by the work of Barbara Starfield, a pediatrician and health services researcher who spent her career studying the core elements of primary care from a health policy perspective [25, 26]. Starfield first demonstrated that primary care is strongly associated with better health outcomes and lower health costs after examining data from nations around the world. These same associations were present when her team examined data comparing American states and local communities. Starfield then became interested in distilling primary care to its core elements as a way of measuring its effectiveness in improving population health outcomes. Based on this work as well as the work of many others, the academic principles central to primary care's positive impact on public health constitute family medicine's core academic principles. These are *access*, *continuity*, *comprehensiveness*, *care coordination*, and *contextual care* [23].

Access

Most of the care delivered by family physicians is first-contact care with patients who choose when and how to access that care as opposed to being referred by another clinician. Access to care encompasses the study of how patients make these choices. Family physicians need to understand how barriers to access limit the patient's ability to get the care he or she needs. Also important, however, is the study of why some patients overuse health care and how to manage and modify access. Understanding access to care includes

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office-based care but also addresses how patients use after-hours care, emergency care, the hospital, home care, and end-of-life care.

Continuity

Continuity of care involves the study of how the doctor-patient relationship develops, changes, and ultimately ends. There are at least four dimensions of continuity, including chronologic continuity, geographic continuity, interpersonal continuity, and continuity for families. Continuity can be measured, and its impact on patient satisfaction and health outcomes can be studied. Finally, continuity in the doctor-patient relationship can be adapted and applied to caring for patients within interdisciplinary teams and to caring for families as a group. A rich literature now exists establishing that continuous interpersonal relationships between patients and care teams are central to quality primary care, but these relationships are affected by changes in insurance coverage and by new forms of information and communication technology.

Comprehensiveness

Comprehensive care involves the study of the scope of practice and extent of services delivered by family physicians. This includes an examination of which clinical services are most essential to the health of the community being served. Comprehensive care includes skills in community-oriented primary care and the study of how the scope of services offered by a family physician changes over time. How are family physicians able to care for such a broad range of problems affecting patients of all ages and both genders in the office, the hospital, and the community environment? Which health problems are common, and how does the family physician care for these common problems? Which clinical procedures are performed by family physicians, and how does a family physician determine when to perform a procedure or refer the patient to another specialist?

Care Coordination

Care coordination involves the study of how family physicians organize and manage the care they deliver to patients and communities. This includes the coordination of preventive services, including disease screening and immunizations. It includes a study of how family physicians organize their medical offices and build working health-care teams to care for patients. Coordination of care includes the study of the specialty referral process, chronic illness management, and the organization of care for special patient populations, such as geriatrics.

Contextual Care

Contextual care is the study of how the health-care problems of each patient are understood in the context of the patient's life. Patients present to family physicians with undifferentiated health problems. Sometimes these are best understood in a biomedical context (acute infections, heart disease). In other cases, the psychological context is most applicable to the presenting problem (depression, anxiety). The developmental context might be most important for some patient problems (behavioral problems and disabilities in children), while the family context might be most important for others (family violence and caregiving for the elderly). In still other cases, community, occupational, and social contexts might be most important (racial health disparities and work-related illnesses). Contextual care is the process by which family physicians help patients to define the meaning of the medical problems and illnesses in their lives. This then allows the patient and physician to develop a collaborative plan that factors patient and family values into a strategy for managing problems involving each of these contexts.

Family physicians are bonded by shared beliefs based on these core principles even though there is substantial variability of how they apply from one community to the next. At the heart of each of these values is a close and enduring relationship between patients and those who care

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for them. Thus, r*elationship-based care* forms the philosophical foundation of the specialty, and understanding care relationships over time is the key to understanding family medicine. Ian McWhinney, considered the father of family medicine in Canada, wrote: "In general (family) practice, we form relationships with patients often before we know what illnesses the patient will have. The commitment, therefore, is to a person whatever may befall them" [27].

Current Challenges and Future Practice

Tomorrow's health care will be shaped by today's events. In selecting what family physicians believe to be the most significant influences on future practice, there is a long list that includes the current focus on evidence-based health care, the medical and societal impact of changing demographics, and some events that are occurring now. The following are the trends the authors believe most likely to influence family medicine in the decade to come.

The Unsustainable Cost of Health Care

Health care in America currently consumes nearly one fifth of the nation's economy with costs per capita that are more than double those of most other countries. Concerns about cost have led most countries to enact measures to restrict them, but the United States has depended largely on market forces to work. For the most part, this has mostly involved attempts to change how health insurance works rather than how the care itself is delivered. While most countries have built systems to make sure everyone has access to health care, universal access is still an unfulfilled promise in America. Without universal access, there will always be a temptation to reduce costs by eliminating people from coverage rather than making the care less expensive. In 2010, the United States enacted the Patient Protection and Affordable Care Act (ACA), the most far-reaching overhaul of America's coverage system since the initiation of Medicare and Medicaid in the 1960s. Its fundamental goal was universal coverage, but it remains controversial with widespread opposition in many parts of the nation. But the ACA is about coverage, not about cost containment, and its full implementation risks further exacerbating the cost problem.

The rising cost of health care has impacted both the private and public sectors of the economy. Businesses struggle to afford health insurance for their workers, with more of these costs being passed to workers themselves. Rising government spending on Medicare and Medicaid has crowded out support of social and educational programs that in some cases have more impact on the health of the public that health care itself. As a result, life expectancy is declining in America for the first time in a century and health disparities based on race, ethnicity, and region of the country are unabated. Still meaningful health reform remains elusive even though the cost problem becomes more severe.

The challenge for family medicine in the coming decade will be to somehow be part of the solution to this problem. The first step in doing so will be to make sure we are not part of the problem.

Commercialization of Medicine

As previously mentioned, American health care has steadily evolved from a collection of small businesses to ever larger corporate delivery systems. While this is often touted as a way to make care more efficient, it can also be viewed as a way to resist cost containment. As government and insurance interests implement measures to lower costs, delivery systems evolve to maintain and expand their market clout. The nation's primary care system lies at the heart of this tension. Family physicians can take the lead in stopping medicine from being converted to a commodity, but more and more practitioners are becoming employees of large health systems. Thus, the nation's family physicians are faced with a choice. On the one hand, family physicians can find security in large health systems and in some cases might succeed in

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helping these systems to evolve in ways that will benefit the public. But there is also the risk that patients will become customers of monopolistic health businesses and that family physicians will help these businesses to resist reform. One way or the other, the nation stands at the precipice of unsustainable health-care spending, and health reform is again at center stage in the national political process.

In 1969 family practice's initial objectives were to combat the fragmentation of health care and protect the centrality of relationship-based care. Today, the family physician's new role is to be the patient's advocate in a system that appears to treat health care as a commodity that is sold to consumers for the highest possible price. Family medicine's future is inexorably tied to the health of the American people whose interests are not always served by more health care; health is the goal, not health care. In a world where patients cannot tell the difference between necessary and unnecessary services, the family physician's role as advisor and partner has never been more essential.

Sustaining Family Medicine as a Desirable Specialty Choice

During family medicine's first decade, as many as 25% of the nation's graduating medical students were choosing family medicine residencies. But student interest fell in the 1980s. In the 1990s, the growth of managed care suggested an increased emphasis on primary care, and student interest again increased. For the past two decades, the portion of American's medical student choosing family medicine has consistently fallen below 12% annually even though the absolute number of medical school graduates and the number of residency programs have increased. The number of medical students choosing careers in family medicine is far fewer that what will be required if all of the American people are to have affordable access to care.

Over the course of history, family physicians have sought to fix its workforce problem by influencing medical school admission policies and by reforming medical school curricula. Successful departments of family medicine exist in most medical schools, but the student interest problem remains refractory to the specialty's best efforts. For many in the discipline, this is viewed as an economic problem that can only be fixed by reform in the physician payment system. To others, blaming forces outside of the discipline itself allows family physicians to avoid the kind of deep reflection required to address this problem. There is considerable truth to both arguments.

Family medicine cannot succeed unless in transforms itself into a field that more medical students will want to enter. Many of them are attracted to family medicine's service orientation and commitment to community-based practice. But family medicine often loses students to other disciplines if they are interested in performing procedures, conducting research, or developing focused areas of practice. Family medicine cannot fix the student interest problem by remaining the same as always, but the specialty also cannot simply try to be all things to all students. Medical students today are no less idealistic than they have ever been, but they are also increasingly not representative of the American people. Medical students are less likely to come from rural communities, communities of color, and poor families than those they will ultimately serve. Fixing the student interest problem remains one of family medicine's greatest challenges and will necessarily require major reforms of the medical education process at the most fundamental level.

Information Technology and the Tension Between Personal Care and Population Health

Over the past decade, the most consequential changes in how health care is actually delivered in America resulted from implementing new information and communication technology. Just as the automobile spelled the end of "horse and buggy" travel and the telephone allowed direct communication with the physician without face to face visits, electronic health records (EHRs) and asynchronous communication by e-mail and text message have profoundly changed the practice of

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medicine. For the first several years after EHRs were adopted, the emphasis was on how to put information into these systems. Physicians who were used to dictating notes in the medical record and writing prescriptions had to learn how to use these electronic systems to order tests, create medical record notes, prescribe medications, and communicate with specialists. Today, family physicians have adapted to these changes and are now faced with the challenge of how to use information that can be extracted from these systems. If information is accurately entered, it is now easy to know things about the practice that could not easily be known before. Family physicians can easily learn how many of their patients with diabetes or hypertension are failing to meet their treatment goals. Family doctors can build registries of unimmunized patients and lists of patients with frequent emergency department use. The ability to access such information has increased the specialty's focus on access to and coordination of services, sometimes at the expense of continuity of care and relationship-based care. Knowing these things raises questions about how to improve them, and these efforts require attention to groups of patients, not just individuals. Thus, a major tension now exists between how best to care for individual people and how to improve the care of the overall population being served.

Today, using asynchronous communication, family physicians communicate with patients by e-mail or text message, and patients have access to nearly limitless information about their health concerns. Patients compare the advice they receive from their family physicians with what they read on the Internet. Sometimes, this improves their understanding, but too often, it confuses them. Electronic information and communication systems are here to stay, and the future of family medicine will depend on how to adapt to them while preserving the specialty's traditional values.

Globalization and Global Health Disparities

The first two decades of the twenty-first century have witnessed dramatic globalization in the world economic marketplace. Goods and jobs are increasingly moving freely across national borders, as is information about lifestyle and economic opportunities. Economic and political unrest in areas such as Africa, the Middle East, and Central America has precipitated the movement of refugees and other immigrants into countries in Europe and North America. At the same time, globalized businesses increasingly work across international borders, and markets are less local than ever before in human history. Health care is not immune from these changes as communities become more ethnically and culturally diverse. In addition, local health-care problems are less likely to remain local as the mobility of the population impacts how disease prevalence affects communities. In the United States, billions of dollars are spent annually for anxiety medication, while in other countries children die of infectious diseases for want of a vaccine or an inexpensive antibiotic. Global disparities in life expectancy and population health are striking, and modern communication technology insures that people know about them. One the one hand, this influences patterns of immigration. On the other hand, it raises problems for the countries to which people move. Recent elections in many countries have underscored the public's unease about open immigration.

The impact of these trends on health care is dramatic. Family physicians in developing countries have far fewer resources with which to work than those in first world countries. Family physicians in Europe and North America are seeing patients who come from much different cultures, speak different languages, and have different health problems that they are used to seeing. Although there is substantial resistance to globalization, it is unlikely that these trends will stop anytime soon. So this has substantial impact on both the day to day work of family physicians and on the process by which they are trained. In such an environment, family physicians have an expanded responsibility. Not only must family physicians care for different patients with different problems; they must also help the communities in which they live to adapt to the changing world.

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Finally, there is the global threat of climate change, a threat that is likely to have dramatic impact on both population health and immigration trends. When the specialty started, the focus was on caring for patients in the context of the individual communities in which family physicians and their patients lived. Information and communication technology have shifted family medicine's focus to the health of those communities themselves. But the future of family medicine will require a more global context for care, and family physicians are only now starting to understand how dramatic this change will be.

Caring for the World

Family medicine has been such a positive influence on health care worldwide that society would have had to invent it for the new millennium, if it did not already exist. Despite past predictions to the contrary, family medicine has survived into the twenty-first century. In fact, it has done much more than survive; it has prospered and has had a powerful impact on health-care delivery and medical education worldwide. Family medicine is a rapidly evolving discipline that brings a much-needed social conscience to medicine and is continuingly reinventing itself as it uses innovative methods to expand its service roles. But a central question remains: is family medicine's goal to fit into the larger health-care community or to fundamentally change it? The quality and availability of health care has measurably improved over the specialty's 50-year history, but this has come at a price. Uncontrolled cost and the growing injustice stemming from population health disparities have brought medicine to a critical juncture. Will health care be devoted to actually improving the health of everyone, or will it be a service business focused on its own economic interests and the care of those who can afford to pay for it. No discipline in medicine has a greater role to play in deciding this question than family medicine. Family medicine must remain the specialty that puts people first – first before profit, first when there are ethical conflicts, first before third-party payers, and first before a single-minded emphasis on disease. Family medicine must resist attempts to commodify relationship-based care if the specialty is to retain the trust of those is serves. Family physicians must care for the world one patient and one community at a time. And all physicians should honor family medicine's remarkable history of achievements and recognize its unlimited potential for future contributions to humankind.

Important Internet Sites

www.aafp.org American Academy of Family Physicians
www.theabfm.org American Board of Family Medicine
www.stfm.org Society of Teachers of Family Medicine
www.globalfamilydoctor.com World Organization of Family Doctors

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Culture, Race, and Ethnicity Issues in Health Care

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The need for cultural awareness and cultural sensitivity has never been greater for family physicians. As access to transportation and information sharing broadens to all regions of the globe – and as information is shared nearly instantly – the influence of culture grows and becomes more complex with every passing year. Areas of the United States that saw relatively little change in population for decades have experienced unprecedented change in recent decades.

Although cultural differences are not new, today's family physician has a unique opportunity – and responsibility – to care for the whole person during this period of rapid cultural change. Because cultural groups and their members each have the potential to interpret their world differently, a solid understanding of the underpinnings of culture is necessary to provide safe and effective primary care in today's society.

The Context of Race, Ethnicity, and Culture

The concepts of race, ethnicity, and culture are frequently used interchangeably in clinical settings. Racial distinctions are perhaps most often used as a means of introducing a patient in a clinical presentation. Yet, racial distinctions often have limited clinical utility and, worse, can perpetuate misleading and potentially inaccurate patient stereotypes. Ethnic and cultural factors, by contrast, are less often mentioned in clinical settings even though they can facilitate clinical decision-making to a greater degree.

Race

Physical characteristics (e.g., skin color, facial features, hair type) that are shared by a group of people generally define racial classifications. From these classifications, many make an assumption of a shared genetic heritage that may be intended as useful historic information in clinical settings. Unfortunately, such assumptions are neither useful nor accurate and add little to medical decision-making [1].

Ethnicity

Ethnicity is more useful than the term race in clinical settings. The word *ethnic* is defined in the *Oxford Dictionary* as "the fact or state of belonging to a social group that has a common national or cultural tradition." The word *ethnicity* is derived from the Greek terms *ethnos*, which refers to the people of a nation or tribe, and *nikos*, which means national or nationality. Ethnicity commonly refers to dimensions of race and nationality, as well as concepts included within culture.

Culture

Culture can be described as the social behaviors (e.g., norms, knowledge, skills, and attitudes) of a group of people learned and passed from one generation to the next. Cultural norms are often reinforced by members of the group and can be modified over time. Conclusive statements about culture, therefore, are rarely possible. An individual's affinity to one's culture can be highly variable. This may be determined, for instance, by the amount of time since one's family migrated from one society to another, level of education, or socioeconomic status. In fact, there may be more similarities between two people of the same socioeconomic status who are from different cultures than between two people of the same culture but different socioeconomic status.

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Population Demographic Shifts

The racial and ethnic makeup of the US population is projected to change in coming decades. Nearly 1 in 5 persons in the United States is projected to be foreign born in 2060. By 2044, more than 50% of Americans will belong to a minority group, any group other than non-Hispanic White alone [2]. With this in mind, the traditional Western health care model will be challenged to meet the needs of diverse populations who have differing, at times conflicting, views of health and illness.

Between 2016 and 2060, the Hispanic population is expected to grow from 57.5 million to 111.2 million, an increase of 93%. The Asian population is projected to be the second-fastest growing racial minority group, from 18.3 million in 2016 to 36.8 million in 2060, an increase of 101%. The Black population will grow from 43 million to 60.7 million, an increase of 44%. In contrast, the non-Hispanic White population is projected to diminish by 10%, from 198 million to 179 million [3]. Table 1 illustrates the percentage of the total population each group comprises in 2016 and projection for 2060.

Overall, the U.S. Census National Projections predict a slower growth in population than in the recent past. However, the geriatric population is growing proportionally faster, with 1 in 5 Americans projected to be over age 65 by 2030 [2]. As individuals age, their healthcare needs may be more complex. Primary care professionals will be expected to manage multiple concurrent chronic diseases and understand the unique challenges the older patient faces such as stereotyping, living with rapid technological changes, and learning to access healthcare from multiple settings – from outpatient, inpatient, to long-term care facilities [4].

Table 1 Subgroup percentage of the total population in 2016 and 2060 projections

	2016	2060
Hispanic	18%	28%
Black	13%	15%
Asian	6%	9%
Non-Hispanic White	61%	44%
American Indian and Alaska Native	1%	1%
Other	1%	3%

Health Status of Black or African Americans

Health disparities between Black or African Americans and other racial and ethnic populations are striking. Black Americans experience high rates of infant and perinatal maternal mortality, shorter life expectancy, and overall higher death rates. Cardiovascular disease is the leading cause of death in the United States, and it is disproportionately more common in the Black population. Non-Hispanic Black adults are at least 50% more likely to die of heart disease or stroke prematurely (i.e., before age 75 years) than their non-Hispanic White counterparts [5]. The infant mortality rate for non-Hispanic Black is more than double the rate for non-Hispanic Whites. Rates also vary geographically, which determine the ease of access to high-quality healthcare, education, employment, and other spaces. For instance, the rates of infant mortality are higher in the South and Midwest than in other parts of the country [6]. The prevalence of diabetes among Black adults was nearly twice as large as the prevalence among White adults [7]. These disparities are often due to economic and social conditions that are more common among Black Americans than Whites. For instance, Black adults are more likely to report that they cannot see a doctor due to cost [8].

Health Status of Hispanics

The US Census defines "Hispanic or Latino" as a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin regardless of race. Health disparities impacting Hispanics are projected to increase as the proportion of Hispanics in the United States grows. Hispanics have higher rates of obesity than non-Hispanic whites. The prevalence of adult diabetes is higher among Hispanics, non-Hispanic

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Blacks, and those of other or mixed races than among Asians and non-Hispanic Whites. Prevalence is also higher among adults without college degrees and those with lower household incomes [9]. The Centers for Disease Control and Prevention has cited some of the leading causes of death among Hispanics to be heart disease, cancer, unintentional injuries, stroke, and diabetes. There are health disparities among Hispanic subgroups. For instance, Puerto Ricans suffer disproportionately from asthma, HIV/AIDS, and infant mortality. Mexican Americans suffer disproportionately from diabetes [10].

Health Status of American Indians and Alaska Natives

Health disparities within American Indian/ Alaska Native (AI/AN) populations remain among the most underappreciated health disparities in the United States. Further, AI/AN populations are historically marginalized by our healthcare system. Though the Indian Health Service is charged with serving the health needs of these populations, more than half of AI/ANs do not permanently reside on a reservation and therefore have limited or no access to IHS. As a result, AI/AN disparities persist. AI/AN adults aged 50–75 years who reported being up to date with colorectal cancer screening were 11 percentage points lower than the percentage screened among White adults [11]. In 2010, AI/AN and Hispanic adults had the highest age-adjusted mean number of physically unhealthy days in the past 30 days compared with other racial/ethnic populations. During 1999–2010, drug-induced death rates in the 30–39 year age group were highest among AI/AN compared to other racial/ethnic populations [11].

Health Status of Asian-Pacific Americans

Asian and Pacific Islanders (APIs) make up less than 5% of the total population in the United States. This, combined with the fact that as a whole APIs have lower overall death rates for cancer, heart disease, stroke, unintentional injuries (accidents), and diabetes than other racial/ethnic populations, may contribute to the misperception that APIs are somehow immune to the disparities that impact other groups. Closer analysis reveals, however, that disparities also exist among APIs and in many cases to a much greater degree than other subgroups. APIs account for more than 50% of Americans living with chronic hepatitis B. Despite these high rates, many APIs are not tested for hepatitis B. They are frequently unaware of their infection, and many recent immigrants do not have access to medical services that can help save lives [12]. As a result, chronic hepatitis B associated with liver cancer in APIs is one of the most serious health disparities in the United States.

Health Equity

Health equity means that every individual has a fair and just opportunity to be as healthy as possible. The principles of equity focus on removing obstacles that lead to unjust differences in health status due to socioeconomic status, location, income, education, race, or ethnicity [13]. Addressing the social and physical determinants of health is one of the overarching goals of the Department of Health and Human Services' Healthy People 2020 [14]. In addition to access to health services, access to education, safe and affordable housing, and public safety affect population health outcomes. For example, a favorable neighborhood walking environment confers improved cardiovascular health [15]. In a study of data from the Center for Disease Control and Prevention, the overall trend for health justice – a measure of outcomes independent of race, sex, and income – declined from 1993 to 2017 [16]. For instance, non-Asian ethnic minorities experience higher rates of HIV diagnoses than Whites. However, a lower percentage of Blacks diagnosed with HIV are prescribed antiretroviral therapy; and on average, Blacks and Hispanics have a lower percentage of suppressed viral load. It is important to recognize the complexity of these health gaps. In order to achieve health equity, we must identify areas of disparity to change and implement policies, laws, and systems that serve to reduce inequities.

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At the 1966 Second National Convention of the Medical Committee for Human Rights, Dr. Martin Luther King said that "Of all the forms of inequality, injustice in health care is the most shocking and inhumane." We have made some but not nearly enough progress in reducing the barriers to equitable health care. Primary care professionals can work to eliminate this form of inequality wherever and for whomever it affects.

Special Populations

Health Status of LGBT People

Lesbian, gay, bisexual, and transgender (LGBT) individuals encompass all races, ethnicities, religions, and social classes. The "LGBT" acronym is a general term to refer to a group of people that are diverse with regard to their sexual orientation and gender identity [17]. "Sexual orientation" refers to an individual's erotic, physical, and emotional attraction to the same or opposite sex. "Gender identity" refers to personal association to female, male, or other genders (e.g., transgender) and may be compatible or incompatible with sexual assignment determined at birth. Sexual orientation and gender identity questions are not asked on most national or state surveys, making it difficult to estimate the number of LGBT individuals and their health needs. Research suggests that LGBT individuals face health and social disparities linked to social stigma, discrimination, and denial of their civil and human rights. A long-standing history of discrimination against LGBT individuals has contributed to their distrust of the healthcare system. Compared with their heterosexual counterparts, LGBT individuals have been associated with higher rates of psychiatric disorders [18], substance abuse [19, 20], suicide [21], sexually transmitted diseases (STDs) including HIV, and increase incidence of some cancers [17, 22].

Creating a Welcoming Environment

Studies have demonstrated that LGBT individuals and their families survey their surroundings to determine if they are in an accepting environment [17]. In the primary care outpatient setting, modifying patient intake questionnaires to include a range of sexual orientations and gender identities is one example of creating an inclusive environment for LGBT individuals. Other examples include posting nondiscrimination policies in high-traffic areas and providing LGBT-relevant brochures and reading material, asking questions during sexual history taking in a nonjudgmental open-ended manner, and mirroring the terms LGBT individuals use to describe themselves [17]. Care should be taken to ensure confidentiality and to be mindful of assumptions made about gender identity and sexual orientation. Additionally, physicians should have awareness of specific issues involving LGBT youth and elderly to ensure that appropriate referrals, community resources, and support are available to the patient.

LGBT Youth

LGBT youth are more likely to face negative health and life outcomes than their heterosexual counterparts. Many may face unique challenges including rejection from family and friends, bullying at school from classmates and authoritative figures, harassment, and violence [23]. Nearly 30% of this subgroup had attempted suicide at least once in the prior year compared to 6% of heterosexual youth. In 2014, nearly 80% of new HIV diagnoses in youths were from young gay or bisexual men. Positive environments at school and at home can help all youth achieve good grades, physical, and mental health. Creating a safe and supportive environment will help them thrive. A positive school climate has been associated with decreased depression, suicidal feels, substance use, and unexpected school absences [24].

LGBT Elderly

Compared to their younger counterparts, elderly LGBT individuals grew up in an era of discrimination and less acceptance. In the medical world prior to 1973, homosexuality was listed in the Diagnostic and Statistical Manual of Mental Disorders with treatment modalities including electroconvulsive therapy and castration. LGBT elderly are less likely to have children compared to their heterosexual counterparts and thus have less family supports. Prior to the June 2015

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nationwide ruling for legalization of same-sex marriages in the United States, LGBT individuals did not have access to spousal benefits through Social Security and thus may have been impoverished by the death of a partner [17]. LGBT elderly who lose their ability to live independently and are subsequently institutionalized may tend to conceal their sexual orientation [17, 25].

Health Maintenance and Screening

Care should be taken to ensure that routine health maintenance is offered to LGBT patients such as pap smears, mammograms, cancer screening tests, and immunizations. Sexual behaviors such as anal-receptive intercourse and oral intercourse may predispose LGBT individuals to STDs including HIV/AIDS [26]. STD screening should be offered annually and at shorter intervals for high-risk individuals (e.g., multiple partners, drug use in conjunction with intercourse). Consider urethral, rectal, and pharyngeal testing for gonorrhea and *Chlamydia*. Consider screening for anal dysplasia with an anal Papanicolaou test in men who have sex with men (MSM), HIV infected individuals, or any patient with anogenital condylomas [27]. Preexposure prophylaxis against HIV infection may be appropriate for some at-risk individuals who can adhere to daily therapy. Regular screening for obesity, tobacco use, drug and alcohol use, and depression is also recommended.

Health Status of Deaf People

Hearing loss is the second most common disability in the United States, accounting for approximately 10% of Americans [28]. Out of the 8.8 million North Americans who are deaf, it is estimated that between 100,000 and one million belong to the Deaf community [29]. Of note, "Deaf" (uppercase "D") refers to the culture and community of Deaf people, whereas "deaf" (lowercase "d") refers to the lack of hearing [29]. The US Deaf community is a linguistic and sociocultural minority group that is often overlooked as such. It is distinguished by its preferred use of American Sign Language (ASL) and distinct culture. Members of this community were typically deafened during childhood, around age 3, before the acquisition of English language skills. Individuals who were deafened during adulthood are less likely to be members of the Deaf community as they are more likely to have English language proficiency and communicate orally or through speech-reading [29]. Similar to other linguistic and cultural minority groups, studies have shown health disparities in Deaf individuals related to lower socioeconomic status and literacy levels, altered healthcare utilization, communication issues with their physicians, and misinterpretation of medical treatment [27–29]. In an effort to provide culturally competent care, primary care physicians should be mindful of language barriers and differences in sociocultural norms among Deaf people.

Sociocultural Norms

Similar to other cultural minority groups, Deaf individuals tend to socialize among themselves and have differing social norms compared to the majority population. These differences may result in cross-cultural misunderstanding with hearing individuals during social encounters [30]. For instance, communication heavily depends on visual and tactile cues. It is culturally appropriate etiquette for Deaf individuals to describe and distinguish others based on physical features such as weight, nose shape, and hairline. To seek attention, Deaf individuals may touch one another, bang on tables, and wave in someone's visual field. Although these are all acceptable ways to communicate among the Deaf, it may be misunderstood in hearing culture [30]. Another area of cross-cultural misunderstanding is the difference in conversation structure between the Deaf and hearing individuals. English conversations build up to a main point and then conclude, whereas Deaf conversations immediately address the main point and then take a longer time to conclude the conversation [28]. For example, a physician may initiate a conversation by taking time to build a rapport with the patient before eventually discussing the medical issue and treatment plan and then concluding the visit [30]. In Deaf culture, it would be more appropriate for the physician to

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first discuss the main medical issue followed by clarifying the treatment plan and moving to rapport building toward the end [28, 30]. During conversation, a hearing physician should be mindful to not exclude a Deaf individual from conversation as it is considered offensive. Additionally any environmental sounds, such as a knock on the door, should be communicated [28]. For example, if two hearing individuals in the room are having a side conversation, the conversation should be communicated to the Deaf individual.

Language Barriers

In the United States, the preferred language of the Deaf community is ASL; however, unlike other language minority groups, Deaf people are assumed to have fluency in written English and are often expected to communicate via speech-reading and note writing [29]. This can put a Deaf patient at high risk for miscommunication for several reasons. Written and spoken English are often a second language for those who communicate in ASL. Speech-reading is a difficult skill as most English words appear visually ambiguous on the lips. In the context of lower literacy levels among the Deaf, they may not understand specific written words [30]. Furthermore, Deaf people are less likely to repeat themselves than non-English-speaking immigrants [29]. Physicians who are not fluent in ASL should communicate in simple terms, ensure that patients understand medical recommendations, and work with an ASL interpreter to facilitate communication whenever possible [28, 30].

Health Status of Refugee Populations

Family physicians are likely to encounter refugees in the context of a continuity primary care relationship as well as during medical screening examinations conducted as part of the naturalization process into the United States. In either case, an awareness of – and sensitivity to – the unique needs and experiences of refugees can be extremely helpful. Refugees come from diverse ethnic, cultural, religious, socioeconomic, and educational backgrounds [31].

Since 2000, at least 750,000 refugees have resettled in the United States from over 80 different countries, with 30,000 refugees in 2019. Unlike immigrants who generally *choose* to relocate, refugees are forced to relocate and experience emotional trauma, physical trauma, or both when war, famine, or persecution *force* them to flee their countries of origin. Refugees seldom have time to plan, and frequently the move is unplanned and incomplete. There are patterns of experiences shared among refugees which are observed and may offer some understanding for primary care professionals seeking to offer care to the refugees and their families. In general, the mental health and overall wellbeing of this population are strongly tied to their migration history [31].

Common Presenting Problems

Many refugees seek attention for a variety of health problems, most commonly musculoskeletal and pain, mental and social health problems, infectious diseases, and chronic medical conditions. Evaluation of musculoskeletal problems and chronic pain should assess history of physical trauma or physical labor and prior living conditions that may be contributing factors. When presenting with ill-defined pain symptoms, thorough workups rarely yield an organic cause but should nonetheless include assessment for *Helicobacter pylori*, intestinal parasites, vitamin D deficiency, and imaging when appropriate. Not surprisingly, the mental and social health concerns common among refugees can be highly complex and unfamiliar to many family physicians. Depression, anxiety, and posttraumatic stress are more common in refugees than in the general population, as are social isolation, financial problems, and disability, among other concerns (see ▶ Chap. 65, "Care of the Refugee") [32].

Healthcare Issues of Spiritual and Religious Culture

Over the last 20 years, there has been increasing attention to the role of spirituality in multiple areas of healthcare [33]. A Gallup poll in 2017 revealed

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that 87% of Americans believe in God or a universal spirit [34]. Transcending culture, race, and ethnicity, research studies have demonstrated that many seriously ill patients turn to their spiritual beliefs to cope with their illnesses and make important medical decisions [35]. Though studies suggest that most patients would desire integration of spirituality in their medical care, less than 20% of physicians discuss spiritual issues with their patients [33]. In that regard, equally emphasizing the physical, psychosocial, and spiritual facets of humanity is important in the family medicine approach to healing the patient as a whole.

Understanding the difference between "religion" and "spirituality" is essential to having a meaningful conversation with patients about their spirituality. Religion is typically defined as an organized system of beliefs and observances to worship a God or a group of gods, usually embodied within an institution or organization. Spirituality is defined more broadly to describe the search for an ultimate meaning, a deeper sense of values, and relationship with a higher being and may be expressed through religious or nonreligious frameworks. Religious and spiritual practices in particular have been associated with positive health benefits in numerous research studies [35, 36]. Though spirituality generally leads to positive coping, in some instances it can also lead to negative coping, for instance, when an illness or medical crisis is viewed as a punishment from God or when devout prayer does not result in a miraculous cure [35].

As our nation's population grows exponentially, so does the mosaic of religious communities, spiritual beliefs, and practices. Physician demographics across the United States similarly mirror our nation's cultural and religious pluralism. Secular physicians must be mindful to not undermine the spiritual belief system of their patients. Likewise, religious physicians must be mindful to not impose their own belief system onto patients [36]. Though familiarity with diverse spiritual communities and beliefs would be an asset to the clinical encounter, keeping abreast of the wide-ranging nuances is not expected of physicians. It is however important for the beneficent physician to listen, respect these differences, and understand the impact of spirituality on medical decision-making and coping skills in the setting of illness.

Approach to Spirituality in the Clinical Encounter

Spiritual Screening

Obtaining initial spiritual screening is the first step in assessing a patient's spiritual well-being and identifying spiritual distress. Spiritual distress includes "common, normal feelings of vulnerability, sadness, and fear, to problems that become more disabling, such as depression, anxiety, despair, and existential spiritual crises" as defined by the National Comprehensive Cancer Network [37]. Spiritual screening can guide immediate need for spiritual counseling by a trained chaplain or indication for in-depth spiritual assessment. One spiritual screening tool suggested by a consensus panel of the American College of Physicians [35, 36] uses four questions:

1. "Is faith (religion, spirituality) important to you in this illness?"
2. "Has faith been important to you at other times in your life?"
3. "Do you have someone to talk to about religious matters?"
4. "Would you like to explore religious matters with someone?"

Obtaining a Spiritual History

A spiritual history can be performed as part of a social history during an annual physical exam or follow-up visit for new or established patients. A formal spiritual assessment is essential for older patients, hospitalized patients, patients with chronic medical conditions, and those with terminal illnesses to reveal their coping skills, to elucidate their support systems, and to refer to chaplain services [38]. Several spiritual assessment tools are available to assess a patient's beliefs. FICA (Faith and belief, Importance, Community, Address in care), a validated spiritual assessment tool (Table 2) [39], and HOPE spiritual assessment questions (Table 3) [38, 40] use a

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Table 2 FICA spiritual history tool

F	**F**aith and belief	"Do you consider yourself spiritual or religious?" or "Do you have spiritual beliefs that help you cope with stress?" If the patient responds "No," the healthcare provider might ask, "What gives your life meaning?"
I	**I**mportance	"What importance does your faith or belief have in our life? Have your beliefs influenced how you take care of yourself in this illness? What role do your beliefs play in regaining your health?"
C	**C**ommunity	"Are you part of a spiritual or religious community? Is this of support to you and how? Is there a group of people you really love or who are important to you?"
A	**A**ddress in care	"How would you like me, your healthcare provider, to address these issues in your healthcare?"

The George Washington Institute for Spirituality and Health. FICA spiritual history tool. https://smhs.gwu.edu/gwish/clinical/fica/spiritual-history-tool. Accessed August fourth 2015

Table 3 HOPE: Questions for spiritual assessment

H	Sources of **H**ope	"What are your sources of hope, strength, comfort, and peace?"
O	**O**rganized religion	"Are you a part of a religious or spiritual community?"
		"Do you consider your religious or spiritual community supportive?"
P	**P**ersonal spirituality and **p**ractices	"Do you consider yourself spiritual? What are your spiritual beliefs?"
		"Do you observe any spiritual practices? Do you find these practices helpful?"
E	**E**ffects on medical care and **e**nd-of-life issues	"How is your current health affecting your ability to observe your spiritual practices?"
		"Are there any specific observances, rituals, or restrictions that your medical team should be aware of?"

comprehensive series of questions to elicit open-ended discussions on spiritual beliefs with patients.

Spiritual Assessment and Plan

After obtaining a spiritual history and evaluating for spiritual distress, clinicians can document their assessment and integrate their findings into a multidisciplinary treatment plan. Medical management and spiritual interventions are influenced by the nuances of a patient's spiritual beliefs. Areas of special consideration may include:

1. Beliefs, rituals, and practices
2. Attitudes to healthcare staff and illness
3. Diet and fasting
4. Washing and toileting
5. Ideas of modesty and dress
6. Birth and death customs
7. Family planning
8. Blood transfusions, transplants, and organ donation
9. Mental health

Anandarajah and Hight suggest four outcomes following the spiritual assessment [40]:

1. No further action other than offering support, acceptance, and compassion.
2. Incorporate spiritual resources into preventive healthcare. Some examples include meditation, yoga, and listening to music.
3. Integrate spirituality as an adjuvant to medical treatment. For example, a patient may request for scriptures to be read prior to a surgical procedure.
4. Modify the treatment plan. For example, a patient with a terminal illness may decide to forego medical treatment and opt for hospice care.

When the spiritual needs of a patient are beyond a physician's competence or there is a request for in-depth spiritual counseling and prayer, physicians should be attentive to their professional boundaries, and a referral should be made to chaplain services. Most chaplains are expertly trained in listening and communication skills and have specialized knowledge on how

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various spiritual paradigms view healthcare. They may provide or arrange for special rituals and rites directly or act as a liaison with a patient's religious leader. If a patient explicitly requests that a physician prays with them, Post and colleagues suggest that it would be acceptable for a physician to listen respectfully however discourage physician-led prayer unless pastoral care is not readily available [36].

Approach to the Cross-Cultural Clinical Encounter

Several general guidelines have been developed to facilitate cross-cultural clinical encounters. The LEARN model developed by Berlin and Fowkes [40] can identify and resolve issues arising from cultural differences and facilitate communication. The LEARN acronym offers a five-step approach to the cross-cultural interview:

1. *Listen*. The first step of the interview is listening and gaining insight into a patient's perception of illness and treatment. This part of the interview creates a milieu for the physician to "join" with the patient. Questions may include "What is your understanding of your illness?" "What is your understanding of the treatment?" "What are your fears?" and "What is your treatment preference?"
2. *Explain*. After gaining an understanding of the patient's concept of the illness, it is the physician's turn to explain his or her perception of the medical condition. It is important that the physician uses a "Western medicine" or biomedical model for his or her explanation of the illness.
3. *Acknowledge*. After the patient and physician have explained their perceptions of the medical condition, the next step is to acknowledge the patient's explanatory model d highlight areas of agreement and resolve areas of conflict.
4. *Recommend*. During this part of the cross-culture interview, it is important for the physician to incorporate the patient's explanatory model and cultural parameters into the biomedical recommendations. This approach is conducive to acceptance of a treatment plan.
5. *Negotiate*. The last stage of negotiation between patient and physician is a key step to the LEARN model. In this stage, the patient and physician work in partnership to negotiate and develop a treatment plan that fits within a culturally competent framework of healing and health.

Special Considerations

Language and Working with Medical Interpreters

More than 60 million Americans speak a language other than English at home, and of those more than 25 million reported proficiency with English as less than "very well" [41]. As a result, this population is less likely to receive preventive care, have regular care, or be satisfied with their care [42], and they are more likely to have complications from medications, have limited understanding of their medical concerns, and have a greater chance of being misunderstood by their care providers [43, 44].

Professional medical interpreters are trained to interpret the spoken word, in contrast to translators who work with written words. Every effort should be made to utilize trained medical interpreters. Using untrained interpreters is more likely to result in errors, violate confidentiality, and increase the risk of poor outcomes [45]. When working with an interpreter, clinicians should view him or her as a collaborator in providing care for the patient. In addition, to work effectively with the interpreter, the clinician should:

1. Allow extra time for the encounter.
2. Meet with the interpreter first to discuss background, build rapport, and set goals.
3. Look at the patient when speaking; address the patient and not the interpreter.
4. Pay additional attention to body language, as it will precede the interpretation of spoken words.
5. Keep sentence structure simple.
6. Be wary of interpretation provided by family members, and remember that in some cultures, it may be taboo for them to discuss certain topics with their loved ones.

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7. Test for understanding, especially when non-professional interpreters are used.
8. Consider a post-encounter discussion with the interpreter to obtain feedback and make corrections if necessary.

Health Literacy

Conveying patient education and medical instructions to patients with limited English proficiency is challenging. For literate patients, printed patient instructions and educational material should be provided in their preferred language. An effective approach to gauging effective communication and health literacy is to actively involve patients in treatment planning and assessing their understanding through "teach-back." This technique has a prospect of better understanding and adherence to a treatment plan [46].

Time

Different cultures frequently perceive the concept of time in different ways. If allowed to go unrecognized, this difference may present a challenge in the cross-cultural encounter. For some patients, being on time may mean arriving within 15 min or within half a day. For some patients, the concept of an appointment may be foreign or unfamiliar. The concept of future time may also vary. Some patients in rural cultures may have difficulty conceptualizing advice to undertake preventive measures or illnesses that may not exist later or may only exist in an abstract way.

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Family Issues in Health Care

3

Thomas L. Campbell, Susan H. McDaniel, and Kathy Cole-Kelly

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Caring for families remains one of the defining characteristics of family medicine. From the change in our discipline's name from general practice to family practice in the 1960s, family-centered care has been central to clinical practice in family medicine. Over the past decade, the role of the family in health care has evolved with the patient's natural support system becoming increasingly important in the era of health-care reform.

Despite rapid societal changes in its structure and function, the family remains the most important relational unit as it tends to individual members' most basic needs for physical and emotional safety, health, and well-being. As such, family members, not health professionals, are the first and most frequent providers of health care. Outside the hospital, health-care professionals give advice and suggestions for acute and chronic illness, but the actual care is decided upon and

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usually provided by the patient (self-care) and family members. Additionally, chronic illness requires families to adapt and change roles to provide needed care. The aging of the population has led to a significant increase in the prevalence of chronic illness and disability along with a rise in family caregiving.

In this chapter, the term "family" refers to the patient's natural support system – any person defined by the patient as significant to their well-being and their health care, and "any group of people related either biologically, emotionally, or legally" [1]. This includes all forms of traditional and nontraditional families, such as unmarried couples, blended families, and LGBTQ couples. The relevant family context may include family members who live a distance from the patient or other groups such as all the residents of a community home for the developmentally delayed persons.

Role of the Family in Health and Illness

Humans evolved as highly social beings. As such, our close social relationships have a powerful influence on our physical and emotional health. Close supportive relationships have been shown to account for a 46% increase in survival, equal or greater than traditional biomedical risk factors such smoking, diet, and exercise [2]. For children, the closest and most influential relationship is with his or her parents, and for adults, the relationship with one's spouse or intimate partner has the greatest influence on overall health. Supportive close relationships can promote health by reducing stress and promoting emotional well-being and healthy behaviors. In general, married individuals have better mental and physical health than unmarried people across a wide variety of health conditions, including cardiovascular disease, cancer, and stroke [3]. Negative or hostile close relationships have a damaging effect on health through direct biological or psychophysiologic pathways and harmful health behaviors [4].

Close family relationships have been shown to influence multiple biologic systems, including neurologic, endocrine, cardiovascular, and immunologic systems [5]. Marital stress and conflict has been shown to negatively affect the hypothalamic-pituitary-axis (HPA), leading to abnormal rises in serum cortisol and lower levels of oxytocin. These physiologic changes appear to result in increased levels of chronic inflammation and reduced immunity, both of which are associated with poor disease outcomes. Marital distress is associated with a higher risk of developing metabolic syndrome and diabetes in men and women. Depression and obesity appear to play a mediating role in this connection.

Over one-third of all deaths in the United States can be directly attributable to unhealthy behaviors, particularly smoking, lack of exercise, poor nutrition, and alcohol abuse, and are potentially preventable. These unhealthy behaviors account for much of morbidity or suffering from chronic illnesses, such as heart disease, cancer, diabetes, and stroke. Health habits usually develop, are maintained, and are changed within the context of the family. Unhealthy behaviors or risk factors tend to cluster within families, since family members tend to share similar diets, physical activities, and use or abuse of unhealthy substances, such as smoking or drinking. The World Health Organization [6] characterized the family as "the primary social agent in the promotion of health and well-being."

Despite societal changes, families still tend to eat together, share the same diets, and consume similar amounts of salt, calories, cholesterol, and saturated fats [7]. If one family member changes his or her diet, other family members tend to make similar changes. However, most dietary interventions are directed at individuals with little or no attention to the rest of the family. Obesity is a major public health problem. Over 30% of the population is considered obese (more than 20% over ideal body weight), which contributes to numerous chronic illnesses, including diabetes, hypertension, coronary heart disease, and arthritis. Overeating and obesity can play important homeostatic roles in families. The parents of obese children are less likely to encourage exercise and more likely to encourage their children to eat than other parents. Obesity programs that involve the patient's spouse or the child's family

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have better outcomes, especially with long-term follow-up [8, 9]. The family plays an important role in both the development and the treatment of eating disorders such as anorexia nervosa and bulimia [11].

Smoking causes over 350,000 deaths per year, mostly from heart disease and cancer, and remains the number one public health problem in the United States. Smoking is strongly influenced by the family. Adolescents are five times more likely to start smoking if a parent or older sibling smokes. Smokers tend to marry other smokers, to smoke the same number of cigarettes as their spouse, and to quit at the same time. Smokers married to non- or ex-smokers are more likely to quit and remain abstinent. Support from the smoker's partner or spouse is highly predictive of successful smoking cessation. Specific supportive behaviors such as providing encouragement and positive reinforcement predict successful quitting, while negative behaviors such as nagging or criticism predict failure to quit or relapse. The Agency for Healthcare Research and Quality (AHRQ) recommends family and social support interventions as components of effective smoking cessation [10].

Meta-analyses and systemic reviews have demonstrated that interventions that involve a family member generally have better outcomes than individual interventions across a range of conditions for both adults and children [8, 11]. These interventions can be conceptually divided into those that tend to focus on the illness and provide family psychoeducation on how best to cope with or manage the illness and those that focus more on family relationships and how to improve communication and conflict resolution as a pathway for improved coping with the illness. Overall, Chesla [8] found that the psychoeducational interventions decreased overall mortality when compared to usual care. For adults, the most commonly studied illnesses were dementia, cardiovascular disease, and cancer. For children, the strongest evidence supports family interventions for childhood obesity and Type 1 diabetes. Overall, this research supports the families have a powerful influence on health, and family interventions can improve health outcomes.

Challenges to Family-Centered Care

In the 1990s, there was a surge of interest in the role of the family in family medicine. Several major textbooks and numerous articles on family-centered and family-oriented medical care [1, 12, 13] were published and used in medical schools and family medicine residencies across the country. The Society of Teachers of Family Medicine sponsored a well-attended Family in Family Medicine Conference where the latest approaches to working with families in primary care and teaching family-centered care were presented and discussed. Interest in the family in family medicine seemed to decline in the early 2000s with the end of the Family in Family Medicine Conference and a decline in publications on the family in family medicine. There are many possible reasons for this decline in interest and focus.

Over the past two decades, there has been pressure on family physicians and other primary care physicians to see more patients under the current fee-for-service reimbursement system. Many primary care physicians complain that they have less time with patients and feel like they are on a "hamster wheel" having to work faster and faster. Having less time for individual patients has meant little time for families, whether it is meeting with family members during a routine office visit or a family conference.

In addition, the scope of practice of family physicians has been narrowing. The percentage of family physicians who deliver babies has been steadily declining and currently is around 15%. Furthermore, according to data from the American Board of Family Medicine [14], the number of family physicians who care for children has declined from 77% in 2000 to 67% in 2009. Some of this decline is due to aging of the family medicine workforce and subsequent aging of the patients in their practices, as well as the rising number of pediatricians at a time when the birth rate is flat. As family physicians deliver fewer babies and take care of fewer children, the goal of caring for the entire family recedes.

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The Role of the Family in Health-Care Reform

Despite these challenges, there has been a resurgence of interest in family-centered care, in part due to health-care reform. The health-care system is in the midst of an enormous change, transitioning from a fee-for-service system of reimbursement to a value-based model. With a value-based system of reimbursement, clinicians and health-care systems are paid for the outcomes they achieve, rather than procedures they perform. With these changes, there are new incentives to prevent illness and keep patients and families healthy and out of the hospital. Clinicians can be paid for spending extra time with families and family caregivers to prevent hospitalization and other expensive interventions.

As CEO of the Institute for Healthcare Improvement, Don Berwick, MD, first proposed the concept of the Triple Aim: better patient experience, better health outcomes, and lower costs. The Triple Aim has become the primary goal of health care in the United States. Patient and family-centered care has become a major focus of most health-care institutions. Medicare now bases a portion of its reimbursement on patient and family satisfaction of their care. More hospitals and practices are starting patient and family advisory councils to help guide health-care policies. As our health-care system continues to move from fee-for-service to value-based care where outcomes matter, family involvement and family satisfaction will play an increasingly important role.

Family-Centered Care

Since family physicians meet with individual patients more often than with family members, having a family-centered approach regardless of whether seeing an individual or a family is an important skill. This approach complements a patient-centered approach in which the physician explores the patient's experience of illness. The patient's presenting complaint can be thought of as an entrance or window into understanding the patient in the context of the family since the illness experience inevitably occurs in a family or relational context. By exploring the patient's symptoms and illness in context, the physician can learn more about the patient's family, its relationship to the presenting complaint, and how the family can be used as resource in treatment. A key to being family centered is choosing appropriate questions to learn about the psychosocial and family-related issues without the patient feeling that the physician is intruding, suggesting that the problem is "all in your head," or blaming the patient or the family. In a qualitative study of exemplar family physicians, Cole-Kelly and colleagues examined the core components of a family-centered approach with individual patients [15]. These family physicians used both global family questions, "how's everyone doing at home?" and focused family-oriented questions, "how is your wife doing with that new treatment?" The exemplar physicians frequently inquired about other family members and were able to keep a storehouse of family details that they frequently interspersed in the visits.

A risk of being family centered with an individual patient is getting triangulated between family members – having a patient speak to the physician about another family member in a conspiratorial way that invites side-taking. In Cole-Kelly's study, the exemplar physicians were sensitive to the dangers of inappropriately colluding in a triangulated relationship with the patient and were facile at avoiding those traps. The exemplars seemed to have an appreciation for the importance of understanding the concept of developing a "multipartial alliance" with all family members, rather than becoming triangulated. The exemplars often explored family-oriented material during physical exams or while doing procedures, thus not using extra time for these areas of inquiry. Visits with high family-oriented content occurred 19% of the time, while family-oriented talk was low or absent in 52% of the visits. The visits that had the highest degree of family-oriented content were chronic illness visits and well-baby/child visits.

Asking family-centered questions can metaphorically bring the family into the exam room

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and provide a family context to the presenting problem [16]. Examples of family questions include:

- **Has anyone else in your family had this problem?** This question is often part of obtaining a genogram. It not only reveals whether there is a family history of the problem but how the family has responded to the problem in the past. The treatment used with one member of the family or in a previous generation may be a guide for the patient's approach to his/her illness or may describe how a patient does not want to proceed.
- **What do your family members believe caused, or could treat, the problem?** Family members often have explanatory models that strongly influence the patient's beliefs and behaviors regarding the health problem and how it should be treated. If the physician's treatment plan conflicts with what important family members believe or have recommended, it is unlikely the patient will comply.
- **Who in your family is most concerned about the problem?** Sometimes, another family member may be the one most concerned about the health problem and may be the actual "customer," the one who really wants the patient to receive care. When the patient does seem concerned about the health problem or motivated to follow treatment recommendations, finding out who is most concerned may be helpful in creating an effective treatment plan.
- **Along with your illness (or symptoms), have there been any other recent changes in your family?** This question is a useful way to screen for other additional stressors, health problems, and changes in the patient's family and how it is affecting the patient.
- **How can your family be helpful to you in dealing with this problem?** Discovering how family members can be a resource to the patient should be a key element of all treatment planning.

These questions can be integrated into a routine office visit with an individual patient and provide valuable family information relevant to the problem.

Genograms

Genograms, or family trees, are one key to family-centered care. They are the simplest and most efficient method for understanding the family context of a patient encounter (see Fig. 1), providing a "psychosocial snapshot" of the patient. Genograms also provide crucial information about genetic risks and any family history of serious illnesses. With advances in genetic research, a detailed genogram should be an essential component of every patient's medical evaluation and database [17, 18], ideally integrating genetic and psychosocial information.

Genogram information can be collected at an initial visit with more added during subsequent encounters. The genogram may be quite simple and only include the current household and family history of serious diseases, or it may provide more detailed information about family events and relationships. When possible, the genogram should include family members' names, ages, marital status, significant illnesses, and dates of traumatic events, such as deaths.

Obtaining a genogram can be a particularly effective way to understand the family context and obtain psychosocial information from a somatically focused or somatizing patient. These patients often present with multiple somatic complaints and try to keep the focus of the encounter on their physical symptoms and distress. The problems are challenging, and it is often difficult to obtain family or psychosocial information from them. A genogram representing the family history provides a way to step back from the presenting complaints to obtain a broader view of the patient and his/her symptoms in a manner that is acceptable to the patient.

While there are efforts to create digital genograms and integrate them into the electronic medical records, this is not available for most Electronic Health Records (EHRs). Currently, the best option is to create the genogram on paper, scan it into the EMR, and use a bookmark

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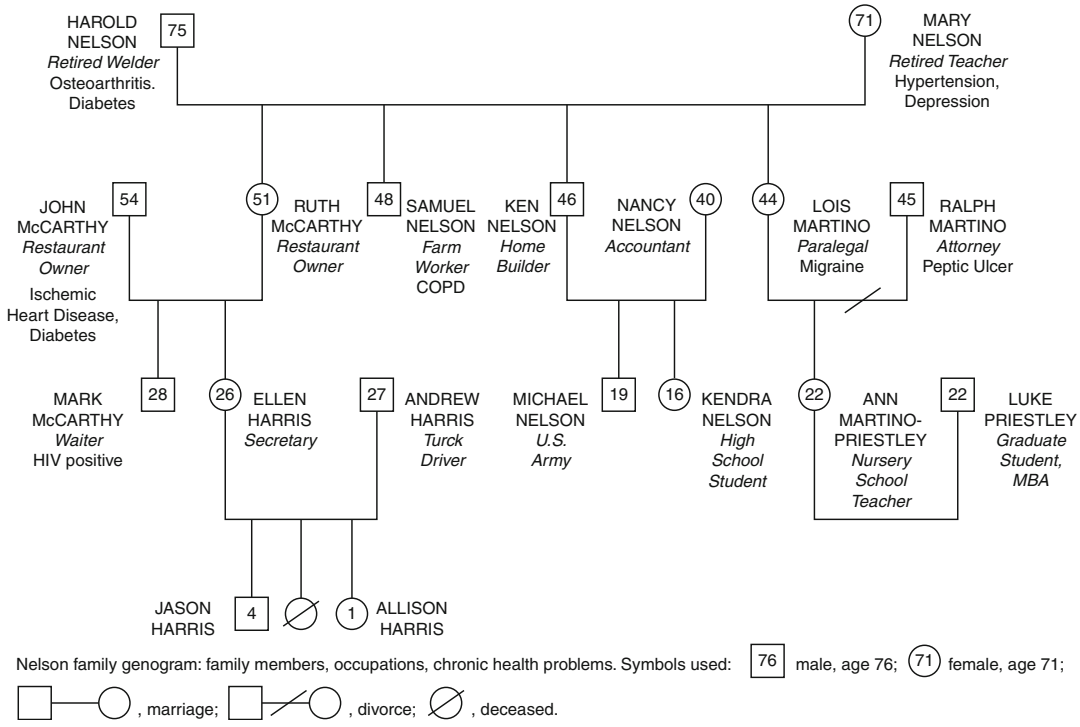


Fig. 1 Genogram

or similar system to easily identify its location. Gone are family folders in which the charts of family members are included in one folder and can be consulted during an office visit. None of the major EHRs have methods for linking the electronic records of family members or even ways to identify related members of a family or household. Clinicians must often rely on household addresses to determine family members.

Meeting with Family Members

Routine visits, in which one or more family members are present, are common and may be initiated by the patient, family members, or clinician. These visits allow clinicians to obtain the family member's perspective on a problem or treatment plan and answer the family member's questions. Family members accompany the patient to office visits in approximately one-third of all visits, and these visits last just a few minutes longer than other visits [19]. In some situations, they may be more efficient and cost effective than a visit with an individual patient since a family member can provide important information about the health problem or the visit may prevent later questions. Family members may serve various roles for the patients, including helping to communicate patient concerns to the doctor, helping patients to remember clinician recommendations, expressing concerns regarding the patient, assisting patients in making decisions, and reporting on the feasibility or acceptability of the treatment plan. Physicians report that the accompanying family members improve their understanding of the patient's problem and the patient's understanding of the diagnosis and treatment.

There are many situations when a family physician may want to invite another family member to the next office visit. Partners and spouses are routinely invited to prenatal visits. Fathers and coparents should be invited to well-child visits, especially when the child has a health or behavior problem. Whenever there is a diagnosis of a serious medical illness or concerns about adherence

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to medical treatments, it is helpful to invite the patient's spouse or other important family members to come for the next visit. Elderly couples are usually highly dependent on each other. It can be particularly effective and efficient to see them together for their routine visits. Each can provide information on how the other one is doing and help with implementation of treatment recommendations. Consulting with family members during a routine visit is advised whenever the health problem is likely to have a significant impact on other family members or when family members can be a resource in the treatment plan.

Principles of Family Interviewing

The principles of interviewing an individual patient also apply to interviewing families, but there are additional complexities. Important Dos and Don'ts of family interviewing include:

DOs
- Greet and shake hands with each family member
- Affirm the importance of each person's contribution
- Recognize and acknowledge any emotions expressed
- Encourage family members to be specific
- Maintain an empathic and noncritical stance with each person
- Emphasize individual and family strengths
- Block persistent interruptions

DON'Ts
- Let anyone monopolize the conversation
- Let family members speak for each other
- Offer advice or interpretations early in a family meeting
- Breach patient confidentiality
- Take sides in a family conflict, unless someone's safety is involved

One must engage and talk with at least one additional person, and there is opportunity for interaction between the patient and family members. In general, the physician must be more active and establish clear leadership in a family interview. This may be as simple as being certain that each participant's voice is heard: "Mrs. Jones, we haven't heard from you about your concerns about your husband's illness. Can you share those?" to directing traffic with a large and vocal family, "Jim, I know that you have some ideas about your mother's care, but I'd like to let your sister finish talking and then we'll hear from you."

When interviewing families, establishing rapport and developing a positive working relationship with each family member is particularly important. In a family systems approach, this is known as "joining." An essential component of joining is making some positive contact with each person present so that each feels valued and connected enough to the physician to participate in the interview. Family members have often been excluded from health-care discussions and decisions, even when they are present. They may not expect to be included in the interview or to be asked to participate in decision-making, even though the conversations at home may be very lively. By making contact with each person, the physician is making clear that everyone is encouraged to participate in the interview.

It is important to join with family members at the beginning of the interview as the physician often has a much more established relationship with the patient. Without this, the family member may either feel left out or as if he or she is merely an observer. One example of this occurs commonly during hospital rounds when there is a family member by the bedside. The usual approach is to either ask family members to leave during the interview or to ignore them. This is both disrespectful and misses the opportunity to use family members as a resource. To avoid this, the physician should greet and shake hands with each family member and find out something about each person, including the family member's relationship with the patient and involvement in the patient's health problems. It may also involve thanking them for their presence and help.

In addition to establishing rapport, the physician can also make use of nonverbal strategies to enhance the relationship with the patient and family members. Just as it is important to be sure

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that the physician and an individual patient are in a comfortable sitting position and at eye level with one another, so it is important that other family members are sitting near enough that they can hear what's being said and be easily seen by the physician. This proximity will help the physician make eye contact with each person in the room. Upon entering the room and seeing that one family member is sitting very far from the physician or isolated from other family members, the physician can gently motion the person to come closer to enhance the sense of everyone being included in the patient visit and being an important part of the encounter.

All the principles of good medical interviewing can be extended to family interviewing. It is helpful to encourage each family member to participate and to be as specific as possible, when discussing problems. Individual and family strengths should be emphasized. Emotions that are present in any family member during the interview should be recognized and acknowledged. ("Mr. Canapary, you look upset. Is there anything about your wife's health or her medical care that you are concerned about?") In addition, the physician must take an active role in blocking persistent interruptions and preventing one person from monopolizing the conversation.

Establishing a positive relationship with family members is particularly important and more challenging when there is significant conflict in the family. When this is the case, it is not unusual for a family member to assume that the physician has taken the side of the patient in the conflict. The physician must take extra steps to join with each family member and establish one's neutrality. An exception to this goal is when family violence threatens and then safety must be the first priority.

Similarly, one family member might dominate both the verbal and nonverbal space in the encounter, making it difficult for the other family members to have as much involvement with the patient or physician. For these cases, the physician must "direct traffic," so all voices can be heard.

It is very easy for the physician to unwittingly be pulled into unresolved conflicts between family members. In the case of an ill child, one parent may try to form a relationship with the physician that excludes the other parent. Or, a wife can try to get the physician to side with her, hoping that the physician's alliance will bolster her position against her husband. To avoid getting caught in the middle of a triangle, the physician needs to be facile at reassuring each member of the family that he/she is there to hear each person's story but will remain neutral. Furthermore, the physician can assert that it won't be helpful to the family if he/she takes sides with one member against another. The physician can emphasize the importance of everyone working together as the most beneficial way to enhance the health care of the patient.

Confidentiality

When working with family members, the family physician must maintain confidentiality with the patient. Prior to speaking with a family member, it is important that the physician is clear about what the patient feels can be shared and what, if anything, cannot be. A family member may bring up difficult or awkward concerns, but the physician may only disclose information the patient has approved (unless that patient is incompetent). In most cases, patients will agree that their care plan can be fully discussed with the family members. However, in family meetings involving adolescents or divorced parents, the "rules" for the meeting need to be clearly spelled out. The physician may remind families at the beginning: "John has agreed that I can talk with you about the options for his diabetes treatment. He, of course, will be the one who will make the final decisions, but we both think it will be helpful to have all of your thoughts about what may be best." Such discussions value both the doctor–patient relationship and the patient-family relationships. The positive support of these relationships is only one of the positive outcomes of well-crafted family meetings.

Conclusion

Health-care reform, the aging of the population, the recent pandemic, and advances in medical research will continue to have a dramatic impact on family issues in health care. There are

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increasing demands on families to provide care for each other, especially aged and chronically ill patients, often without adequate services or insurance reimbursements. Family caregiving has led to increasing burden on family members and poor physical and mental health for many caregivers. The role of the family in end-of-life decision-making is only beginning to be addressed. Health-care proxy laws allow patients to identify an individual, usually a close family member, to make medical decisions if the patient is unable to, but little research has been done on how patients make these choices, what they discuss with their designated health-care agent, and whether family members follow the wishes of the patient. Because of the genetic revolution, we have the ability to screen or test for hundreds of genetic disorders, but the impact of this technology on families is just beginning to be examined. Genetic counseling not only needs to address the genetic risks of the individual but the implications for other family members. More family research is needed in each of these areas.

One of the unique and distinguishing characteristics of family medicine is its emphasis on the family. No other medical specialty has a relational or family focus or uses a family-oriented approach. With our changing health-care system, there is increasing recognition of the importance and cost-effectiveness of involving the family in all aspects of medical care. New models of care are being developed that emphasize teamwork, prevention, and collaboration with patients, caregivers, and family members. A family-oriented approach will become an increasingly valued and effective model in the twenty-first century.

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Family Stress and Counseling

4

Marjorie Guthrie, Max Zubatsky, Lauren Redlinger, and Craig W. Smith

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Introduction

Stress is a continually growing concern in our society. The impact of stress on mental health and physical illness can be significant and a major factor in healthcare costs in the United States. A large percentage of Americans report feeling moderate-to-high stress levels on a daily basis [1]. When stress extends to include family and social aspects of one's life, complexities can exist beyond just individual coping of a situation or event. Stress has been seen by both patients and physicians as influencing health outcomes.

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Family stress can be viewed as a disturbance in the ongoing state of a family system. This disturbance can occur both outside of the system (e.g., war, unemployment, natural disaster) and inside the family system (e.g., death, divorce, chronic illness). This systemic stress creates a change in the family's routine functioning [2]. Normative stressors (e.g., birth of a child, job transition, loss of an older adult) in families are considered to be common and predictable sources of stress. Nonnormative family stressors (e.g., early widowhood, job loss, natural disaster) are uncommon and unexpected and may occur at times other than those expected in the life cycle of the family or its members [3, 4]. How well the family unit copes with these two types of stressors largely impacts both the short-term and long-term adjustments and well-being of both the unit and the individuals in it.

Divorce and abuse have been cited as two of the most stressful events that commonly occur in families [5]. Numerous problematic outcomes and life adjustment problems have been found in individuals following divorce. Divorce has long been linked to physical and emotional health problems in adults. Increases in depression, dysthymia, and alcohol abuse have been reported, based on both the quality of the relationship prior to divorce and financial resources of the family [6, 7]. Additionally, intimate partner violence has long-term health consequences for survivors, even after the abuse has ended. The effects of abuse can lead to negative outcomes such as poorer overall health, lower quality of life, and higher use of healthcare services than the general population [8].

Another type of stress that impacts our patients' health is adverse childhood events (ACEs). These events include abuse of the child as well as household dysfunction such as having a parent with substance abuse disorder, spousal violence in the home, and criminal activity in the home. It is estimated that over 50% of adults have experienced one ACE during childhood [9]. The role that events in childhood play on long-term behaviors, health beliefs, morbidity, and mortality continues to be studied. It has been seen that these events are correlated to increased rates of cancer, ischemic heart disease, chronic lung disease, skeletal fractures, and liver disease [10]. If these events are identified, interventions such as trauma-focused CBT and victim-centered services have been shown to improve protective factors [9].

Family strain has an impact on multiple levels of member's lives. The relationship between parental stress and parenting practices can have strong effects on the behavioral outcomes of children. Parental responses to stress can lead to subsequent internalizing and externalizing behaviors in their children, especially those with serious medical or health conditions, such as diabetes [11]. Stress within families also has significant financial and occupational consequences. Work and family are particularly significant sources of stress, given that a large percentage of adults devote large amounts of time to these two areas of life [12]. The high time demands of work environments have strong impacts on the mental, physical, and relational well-being of the worker and their family members [13]. Families who experience financial strain endure the added challenges of obtaining adequate healthcare and other resources. Other internal and external sources of stress can have major ramifications on the adjustment and well-being of members over time (Table 1).

A chronic illness or a medical issue can prompt the onset of family stress in various ways. For example, caregivers of family members with chronic illness often experience high levels of

Table 1 Examples of internal and external family sources of stress

Internal factors	External factors
Death in the family	Natural disaster
Divorce or separation	Community risks/crime
Financial problems or job loss	Lack of access to care/ insurance coverage
Accident/disability/ illness	Migration/immigration
Miscarriage	Economic recession/ depression
New members in the household	Changes in the workplace
Caregiving	War
Abuse/neglect	Political issues

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stress. According to the National Alliance of Caregiving [14], more than half of caregivers in America reported feeling overwhelmed by the amount of care required by an aging or chronically ill family member. Additional life events and stressors can influence a family's ability the cope with a serious or persistent illness. Physicians should view the etiology of family stress from a variety of perspectives and consider its effects on multiple members of the family unit.

Theoretical Frameworks of Stress and Health

Family Systems Theory Framework

For much of the twentieth century, clinical practice of individual symptoms and conditions was largely focused on etiology and considered to be rooted in the psychopathology of the individual. With time, a new systemic paradigm emerged, seeing one's problems as interconnected to other members and relationships in the family system, breaking away from the deterministic, linear, and causal views of individual dysfunction [15]. Bowen [16] further advanced the concept of considering families to be cohesive systems, highlighting the fact that the problems (mental, emotional, or physical) of one individual in a family cannot be understood in isolation from another but rather that the family must be thought of as one emotional unit. Recently, physicians are becoming better informed of the inter-relational and systemic causes of disease and illness, understanding the connections of illness with areas such as family dysfunction, relational stress, mental health issues, parent-child relationships, and spirituality. For families experiencing a member with chronic illness or disability, systems theory not only pertains to the determinants of health within the family system but other relationships with healthcare professionals, insurance providers, and other agencies that may be involved in the patient's care [17].

McDaniel et al. [18] highlighted the following concepts and questions to help physicians apply systems theory into practice with families:

- **The Family as a System: Questions to help identify those in the family.**
  - Who are the members of the patient's family?
  - When it comes to daily support, who does the patient consider as family?
- **Family Stability: Questions to understand the stability of the family.**
  - What does the family do to maintain balance and security for its members?
  - If change occurs too quickly, what will happen to the family's stability?
- **Family Change: Questions to assess the effects of change on the family.**
  - What does the family do to facilitate the needed change?
  - If change does not occur quickly enough, what will happen to the family?
- **The Relational Context of the Symptom: Questions to determine the impact of health concerns on the family.**
  - How do the patient's symptoms influence the family?
  - How does the family influence the patient's symptoms?

Mind-Body-Environment Framework

Antonovsky has been largely credited for being one of the first researchers to explore the physiological response to stress. His work largely focused on the search for health (salutogenesis) rather than pathology (pathogenesis) in individuals enduring situations of extreme trauma. Individuals who have specific dispositions may make individuals more resilient to global stressors on an everyday basis [19]. Antonovsky believed that health, stress, and coping are interrelated factors, and professionals should not focus solely on the factors that cause disease [19]. George Engel [20] gave further attention to biobehavioral health, rejecting the traditional medical model of disease and addressing the importance of exploring the psychosocial dimensions of one's health. According to Engel, areas of one's psychological and social life often have an interchangeable connection to physical health outcomes. The

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boundaries between health and disease, or well and sick, are ambiguous at best. Thus, certain cultural, social, and psychological considerations must be taken into account to define the impact that the stress of illness and disease has on one's life.

Another model of health and stress that has been advanced is the diathesis-stress model [21].

Individuals may be seen to have particular vulnerabilities to stress, given a set of life circumstances both individually and systemically. If the combination of stress and vulnerabilities exceeds a certain threshold, it is more likely that an individual will develop a particular disorder (Fig. 1). The model combines both genetic endowment and environmental factors, along with the reaction to the onset of stressful life events. Certain protective factors (social networks, self-esteem, community) may buffer against the susceptibility to particular stresses that could initiate or exacerbate a given disorder or condition.

These mind-body frameworks are critical for healthcare providers to conceptualize when working with patients and family members. Working from a biopsychosocial model gives physicians an idea of why some individuals view sickness as an "illness," while others may regard these issues as "problems of living." Additionally, physicians can benefit from asking patients and their family members about past stressful events and how they have coped around these events as a unit. Identifying these positive areas of coping around stressful events could provide useful information when establishing treatment goals and in developing suggestions for behavioral and lifestyle changes that patients can make over time.

Health Belief Framework

When individuals make determinations about both short and long term medical decisions, they must often weigh several costs and benefits of their own health. The Health Belief Model theorizes that one's background and personal ideas of their health will impact perceived self-efficacy, which in turn predicts engagement of a certain health behavior [22]. Rooted out of Social Learning Theory [23], the determination of specific health-related actions can be based on sufficient motivation, belief that one will be susceptible to a serious health issues, and the belief that a recommendation would be beneficial to them over time. The model provides a helpful framework of how individual characteristics can influence engagement of certain health behaviors, such as medication adherence, elective surgeries for chronic disease, or vaccinations for influenza.

Developmental Life-Cycle Framework

Families often lack a clear perspective of time when problems or crises occur. Members may be

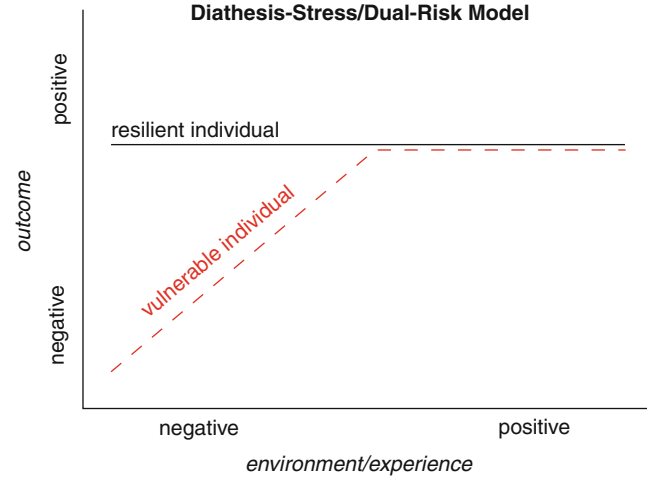


Fig. 1 Diathesis-Stress Model

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stuck in past events, feel immobilized by current situations, or become fearful of possible future events that may occur. From a developmental life cycle framework [24], symptoms and dysfunction in a family system are examined from a systemic perspective. Several stressors have been said to impact the long-term functioning and well-being of members over time. Some stressors derive from family history that is passed down through generations (e.g., secrets, legacies, genetic abilities and disabilities, and religious beliefs and practices). Others are comprised of developmental, unpredictable, and historical events that occur across an individual lifetime (e.g., trauma, chronic illness, accidents, natural disaster, war, and economic circumstances).

Stress may also be transmitted between family members and across generational lines. A family's behavior and response to illness cannot be comprehended apart from its history [25]. A multigenerational assessment of family stress helps to clarify both strengths and vulnerabilities in family members, while identifying "high-risk families" who are often burdened by past unresolved issues. Tracking key events, organizational shifts, and coping strategies around illness can help explain and often predict future coping strategies of the entire system [26].

Having both a developmental and multigenerational lens of patient care broadens the narrative of illness and health-related symptoms across the life span. A useful tool for physicians in the assessment of health and stress in families is the medical genogram (Fig. 2).

Family Response to Crisis Framework

There is wide variation in how families adjust and adapt to a triggering event or crisis. One of the first

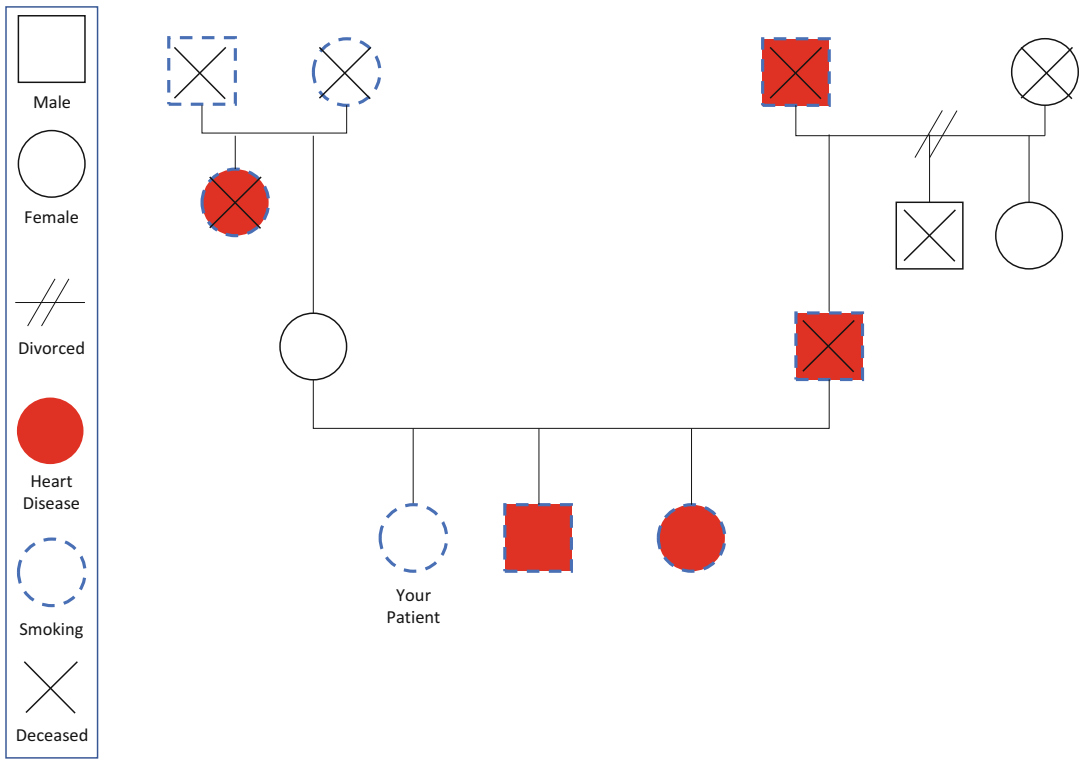


Fig. 2 Medical Genogram: This diagram offers physician a quick way to evaluate health risks, pursue preventative measures or treatment and assess the family history in a more comprehensive and systematic manner. The figure shows how many members of the family have smoked as well as have heart disease. This link could be helpful in further counseling your patient on the importance of quitting smoking

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family stress frameworks to address adjustment and adaptation emerged from Hill's classic work on the family response to war and separation, where he advanced the use of the ABCX family crisis model [27]. Stress is not seen as an inherent characteristic of an event but rather is a function of the family's response to the event and the residual effects over time. Hill hypothesized that when a stressful event or crisis impacts the family unit, the availability of resources and perception of the event will determine the level of stress that the family system will endure. McCubbin and Patterson [28] expanded this model, including a second level of coping and adaptation after a stressor (Fig. 3).

The ABCX model is a useful conceptualization for family physicians when assessing the resources and coping strategies of families after an illness. When families are going through the "crisis period" of an illness, physicians and healthcare professionals can work on normalizing this period of stress and vulnerability in families. This is an important stage that occurs after a patient is diagnosed with a serious or chronic illness and when outside resources and help regarding medical support, medication management, travel, and healthcare access become important factors to consider.

Effects of Stress on Health

Stress can happen inside and outside the family system and it can be normative or nonnormative. The human body is uniquely equipped to handle the demands of an acutely stressful event. The body sets off a series of hormonal responses to prepare the body for action either flight or fight. This response is mediated by the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) working together [29]. These acute responses are lifesaving when confronted with a survival situation. In the current modern lifestyle, the need for an acute response to a life-and-death situation is uncommon; nevertheless, when the body perceives stress of any kind, the same systems are activated and the entire body is affected. The response is intended to be short term. When there is no break in the stress or no perceived break in stress, the acute stress response does not resolve. Chronic stress hormone elevation may then result in significant health problems [29].

Acute Stress

The entire body is affected by heightened hormonal and nervous system responses to an acute

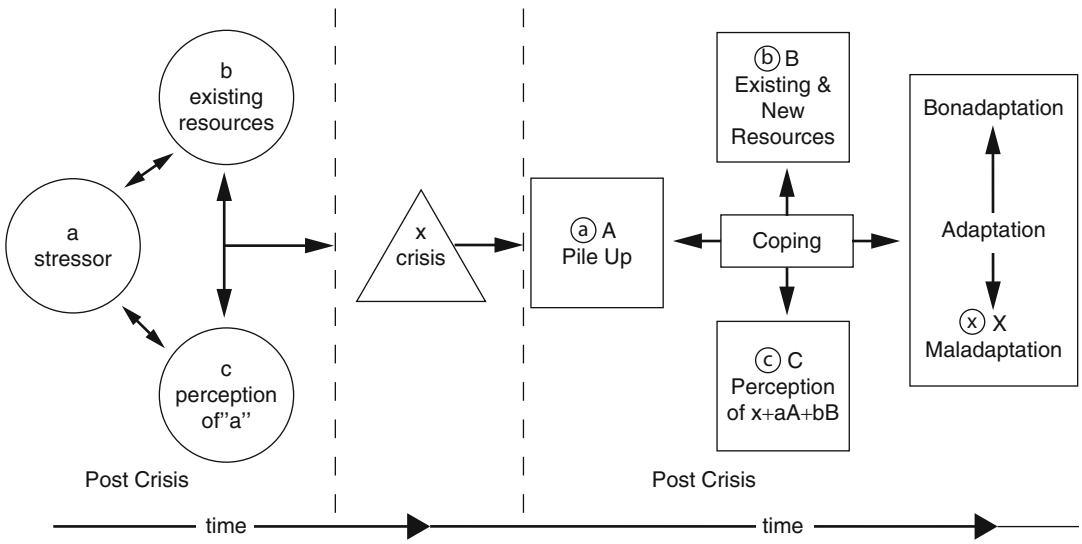


Fig. 3 The Double ABCX Model [28]

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stressful event. The brain and nervous system are significantly impacted. There is an increase in alertness and a sense of anxiety. Short-term memory, concentration, inhibition, and rational thoughts are all suppressed to enhance quick reaction time for the fight-or-flight response. In this state, social and intellectual demands become challenging. The hippocampus is processing long-term memories to discover episodes that might be similar. The brain moves to an increased state of arousal [38]. When activated the adrenals work to release stress hormones. In addition to the hormones that are being produced in the endocrine system, the liver increases blood glucose levels for the energy needed for the fight-or-flight response. The increase state of arousal in the brain results in increase in glucocorticoids as well as norepinephrine. Through the glucocorticoids as well as other neuroendocrine pathways, there is inhibition of the growth hormone pathway, thyroid axis, and reproductive hormones. In the short term, these hormonal changes allow for heightened analgesia, suppression of appetite, and suppression of reproductive axis [29].

The respiratory system responds by increasing respirations to meet the oxygenation demands. This enhances the sense of anxiety and panic that is needed to respond to the flight or fight. The heart and circulation are affected. The heart rate rises and contracts more strongly. Blood pressure rises in response to the acute stress. The blood vessels dilate directed toward large muscles and heart vessels to increase blood flow to those parts of the body that are essential to the fight-or-flight response [29].

As the hormonal and nervous system focuses on the acute needs of the fight-or-flight response, other areas of the body are affected by decreased blood flow. Muscle tension increases as blood supply is diverted to prepare the body for action. The gastrointestinal tract receives less overall blood supply and has a response to the increase in hormones. There is an increase in acid production and sensitivity to heighten hormonal states that can increase epigastric pain and lead to nausea. Lastly in the acute stress state, the reproductive organs are affected. There is decreased blood supply to the genitals [30]. In females, stress hormones interfere with the hormonal regulation of the menstrual cycle. Acute stress can lead to changes in menstrual cycles, menopausal symptoms, and reduced sexual desire.

Once the acute event is resolved, these responses should resolve and return to a resting state. The modern day dilemma is when the perceived acute stress is never resolved, safety is never achieved and the physiologic response changes from an acute state to a chronic exposure to heightened arousal and elevated stress hormone levels. There is growing evidence that these effects exacerbate chronic conditions and may predispose to the development of some chronic conditions such as hypertension or diabetes.

Chronic Stress

The effects of chronic stress can be difficult to study. Studies of the effects of stress can be observed in humans as early as in utero. The effects of chronically elevated cortisol have been observed to result in adverse birth outcomes that include low birth weight, prematurity, and all-cause mortality. In addition, infants born to mothers with elevated cortisol levels also have elevated cortisol, suggesting a lasting effect of stress transferred from mother to child [31].

Chronic stress may have negative effects at any age. A study of post-hip fracture geriatric patients found that those with depression as a marker of chronic stress demonstrated reduced bactericidal functioning of monocytes [32]. There is an increased susceptibility to infections secondary to lower white blood cell counts in response to stress.

Exacerbations of the chronic disease process due to chronic stress are evident in many diseases. Diabetes, for example, is very sensitive to elevated cortisol levels. This leads to insulin resistance and elevated blood sugars [33]. Stress can cause feelings of increased anxiety, which in turn will exacerbate many psychiatric diseases. When left unresolved, stress can lead to chronic anxiety disorders and/or chronic major depression. There is an overall loss of pleasure and accomplishment and the disruption of the serotonin system in the

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brain. Tension headaches, backache, shoulder pain, and chronic pain syndromes can all develop from chronically tense muscles [38].

The increased respiration rate during stress can trigger asthma or COPD exacerbations and worsen respiratory diseases overall. Irritable bowel syndrome has been linked to stress. Those with inflammatory bowel disease can experience increase in flares under stress [30].

Now that we have seen the effects of chronic stress on disease, the question is, can chronic stress cause disease? This is a little harder to make a direct link, but the evidence is growing. In a state of chronic stress, eating habits are affected. When under chronic stress, there is hormonally induced craving for foods high in caloric intact and carbohydrates. Carbohydrate in particular increases tryptophan and can increase serotonin combating the hormonal effects of chronic stress. Chronic exposure to elevated cortisol also boosts abdominal fat and weight gain [29]. There is also a decrease in physical activity after exposure to chronic stress. As depression and anxiety worsen, sleep disorders are exacerbated. Chronic stress may also lead to many negative life choices and leads to an overall increased risk of chronic disease.

Lastly, the evidence that chronic stress has effects on cardiovascular health cannot be ignored. The lifesaving increase in heart rate and blood pressure in an acute stress response loses any benefit when maintained over the long term. It is well established that stress can contribute to the development of atherosclerotic vascular disease, by several mechanisms. There is also evidence to support the possible contribution of an inflammatory response mediated by chronic stress hormones [34]. The coronary arteries are also very sensitive to the stress hormones released during the acute response [29]. The effects go beyond the increase in heart rate and blood pressure. There can be alteration in cardiac rhythms. There is an effect on cholesterol and impaired fat clearance. There is evidence that vessel intima-media thickness increases and there is a release of inflammatory markers into the bloodstream during the stress response (Table 2).

Chronic stress exacerbates many chronic conditions. Chronic stress may lead to negative lifestyle choices that contribute to risk factors for chronic disease. Once acute stress is identified, helping patients manage the acute phase and prevent long-term chronic stress is beneficial to the overall health of all family members.

Counseling Strategies for Patients and Families

By attending to the biopsychosocial framework of health, the patient and family can be helped to minimize the effects of family stress and to

Table 2 The effects of stress by system

System	Acute stress effect	Chronic diseases worsened
Mood	Increase panic	Anxiety and depression
Neurologic	Decreased short-term memory	Dementia
Musculoskeletal	Tension	Tension headaches
		Chronic pain
Respiratory	Tachypnea	Asthma and COPD exacerbation
Cardiovascular	Elevated blood pressure	Hypertension
	Tachycardia	CAD
		ACS
Endocrine	Elevated hormones	Diabetes
	Hyperglycemia	
Gastrointestinal	Constipation	Irritable bowel syndrome
	Diarrhea	Inflammatory bowel disease flares
	Increased gastric acid	GERD
Sexual and reproduction	Male erectile dysfunction	ED
	Female menstrual changes Decrease Libido	PMS
		Menopause

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develop strategies for coping in the future. Physicians could benefit from utilizing specific counseling skills for psychosocial issues beyond routine screening and assessment at visits. Specific approaches such as behavioral techniques, solution-focused strategies, motivational tools, or educational resources can help both patients and families cope with stress-related issues around illness and health. The following highlight these approaches when working directly with the patient as well as the family system.

Individual Treatment Approaches

Motivational Interviewing

Patients and families are often reluctant to change coping mechanisms in response to stress and crisis management that have been developed over time. When a patient or family member feels "stuck in the situation," it may be due to deficient coping techniques or perhaps their perception of the problem. The ways in which physicians and other professionals can talk with patients and families about health and personal issues can influence their motivation to change certain behaviors. Motivational interviewing (MI) is an effective, evidenced-based approach that delivers these therapeutic benefits to patients, family members, clinicians, and healthcare professionals [34]. MI has been found to have numerous applications to chronic illness and health issues (sexual health, weight loss, medication adherence, diabetes) as well as mental health and family-related issues (depression, OCD, alcohol abuse, anger management, domestic abuse).

Healthcare professionals using motivational interviewing should implement the following key steps [35]:

- Assess the patient and/or family member(s) ambivalence about change
- Recognize change talk when you hear it in conversation (e.g., desire, ability, reasons, need, commitment, taking steps)
- Use open-ended questions and reflective listening skills to get more depth of patients' perspectives
- Meet the patient and/or family member(s) at their stage of change around the particular issue

Solution-Focused Brief Therapy

Pressures of time and schedules often force physicians to have suboptimal encounters with their patients, especially in primary and ambulatory settings. Patients may have limited time to provide in-depth information on their presenting problems and tend to focus solely on complications and symptoms rather than strategies and solutions. Solution-focused brief therapy (SFBT) has become a helpful intervention approach for patients and family members to recognize strengths in order to reduce the intensity of symptoms and identify solutions [36]. Behavioral health professionals and other providers who use this approach ascribe that patients possess the necessary skills needed to improve their lives, but may need help remembering times that they have coped with a particular problem successfully. Solutions are seen as different ways of viewing their lives, that their problems are not to be solved by professionals, but that solutions are mooted and discovered primarily by the patient and/or family [36].

Healthcare professionals using solution-focused brief therapy should implement the following key steps:

- Helping patients and family member(s) recognize the times when stress around the illness, disease, or issue was reduced or did not exist
- Identifying a list of resources and strengths that the family already has available
- Cocreating a treatment plan, where the patient, family, and provider are working together on outlining goals
- Developing small, attainable goals that the patient and family can achieve over time

Cognitive Behavioral Therapy

For some patients, interventions around behavior changes and improved cognitive awareness are warranted to improve health outcomes. Professionals may choose to deliver advice and treatment planning that is more directive and behaviorally oriented in nature. Cognitive behavioral therapy (CBT) is a widely utilized behavioral intervention in medical settings around not just chronic or life-threatening conditions but for self-regulation and stress reduction around mental

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health and family-related stress. Although behavioral approaches can provide effective outcomes for patients and families, this therapy modality has been largely underutilized in primary care. One reason may be the time-limited environments that physicians typically work within [37].

Healthcare professionals using cognitive behavioral therapy should implement the following key steps:

- Support the thoughts, feelings, and emotions of patients and families working through an illness or stressful life event
- Identify certain triggers or barriers that impact negative thoughts and reactions to presenting problems
- Set behavioral goals, where the family can learn to reduce maladaptive behaviors in a time-limited fashion

Mindfulness Based Stress Reduction

When stressful triggers or life events arise, patients need to attend not only to their cognitions and thoughts but also physical symptoms throughout their body. Physicians can reduce the patient's stress or worry of future events and situations but using interventions of awareness and attunement to focus on the "here and now." Mindfulness work is an effective process where one's awareness is on the present moment, paying close attention to the thoughts, feelings, bodily state, and environment around them [38]. In patient and family care visits, this intervention is about teaching individuals how to respond to stressful events more reflectively instead of reflexively. Mindfulness-based stress reduction (MBSR) has integrated meditation work into psychological and family-related issues with patients. Originally, MBSR was a group-based program that helped patients suffering from severe chronic pain and stress-related symptoms, but can be utilized by individuals.

Healthcare professionals using mindfulness should teach patients the following key steps [39]:

- *Body scan*: gradual attention throughout the entire body, focusing on sensations through body regions with periodic breath awareness and relaxation strategies
- *Sitting meditation*: mindful attention of breathing and a state of nonjudgmental awareness of cognitions and thoughts
- *Yoga practice*: breathing exercises, simple stretches, and posture work that is intended to strengthen and relax muscles

Family Treatment Approaches

Family Psychoeducation

Low levels of health literacy can lead to increase individual and family stress. Misunderstanding and miscommunication of health-related information also add to the stress of patients and families dealing with health concerns. Psychoeducational interventions can help educate patients, family members, and caregivers about the specifics of an illness or condition, as well as what areas the family can help provide additional care. This information offers families additional resources to cope around a particular crisis event or diagnosis and provides general problem-solving skills. Particular guidelines [40] can be delivered around illness management, medical adherence, and assistance with daily issues, and expansion of the patient/family member's social network is emphasized. Many psychoeducational interventions given to patients, family members, and other caregiver individuals are not delivered by behavioral health professionals [40].

Healthcare professionals using psychoeducation should implement the following key steps:

- Ask the patient and/or family member(s) what they know about the issue and what professionals have discussed the issue with them
- Deliver basic information in clear and understandable terms for everyone to understand
- Allow for the family to ask follow-up questions or clarify any unfamiliar words, terminology, or medical jargon
- Provide literacy-appropriate health education materials

Intergenerational Approach

Stress in families can be transmitted through multiple generations, where individual family

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members have been unable to cope with life events. Bowen's theory [25] was a way to observe the emotional unit of a family, observing these systems on a continuum, ranging from extremely impaired to high functioning. When anxiety and stress occur in a family system, members will adjust the amount of dependence they have on each other to attempt to resolve the given crisis or situation. This therapeutic approach looks at the family system beyond just symptom reduction, exploring how the family will be able to function in a more healthy fashion around a stressful event such as illness or disability.

Healthcare professionals using an intergenerational approach should include:

- **Level of differentiation in family members**: Members with a well-differentiated "self" can stay calm and clear headed in the face of anxiety and stress. Poorly differentiated members have to rely heavily on these members during times of crisis.
- **Triangulation**: A triangle is a three-person relationship system and the smallest stable relationship system. During times of stress or crisis, two members may pull a third person into their subsystem to resolve a conflict or to mediate tension.
- **Family projection process**: This describes the primary way that parents transmit their emotional turmoil and feelings onto their child. This process can impair the functioning of multiple children and cause onset of clinical symptoms.
- **Emotional cut-off**: This concept describes how individuals manage their unresolved emotional issues with parents, siblings, or family members by completely cutting off ties with the person or group.

Group Treatment Approaches

Dialectical Behavioral Therapy

Patients who have more significant mood or personality disorders often need techniques on how to regulate their emotions more effectively. Dialectical Behavioral Therapy (DBT) is an evidenced-based approach to help individuals increase their emotional and cognitive regulation by learning how to cope with reactive states. DBT has been implemented in several clinical sites where both adults and teens can benefit from a group approach to emotional regulation [41]. Participants in DBT groups practice four domain areas: mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness. Group sessions normally meet once per week to help learn specific skills and apply them around the four domains.

Psychodynamic Group Therapy

Often, patients with similar diagnoses need to have a space to share their inner thoughts and experiences of their condition with others. Those who may be suffering with a similar diagnose such as depression, attention deficit hyperactivity disorder, or bi-polar disorder often benefit from psychodynamic group therapy [42]. The group is led by one or two mental health professionals, where the facilitators help group members learn about some of the dysfunctional patterns of the condition they're experiencing. Each group member takes the role of a mental health healer to their peers, where the group learns about unhealthy patterns of behavior through talk therapy.

Psychoeducational Groups for Families

Psychoeducation is an effective way to inform patients and family members about a particular issue or concern in a clinical setting. Groups offer a combination of cognitive techniques and information so that members will derive considerable growth and understanding of coping with this illness or condition [43]. These groups are led by an experienced therapist who is goal-directed and structured in their technique. Group members take the role of learners around a number of conditions such as depression, diabetes, cancer, or anorexia.

Caregiver Well-Being

Providing care to a loved one often has significant impact on one's life. Between 20 and 44% of caregivers say that providing care is financially, physically, and emotionally difficult on a regular

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Table 3 Therapist Types. There are several categories and types of therapist. This list presents a summary of the most common [47]

Category	Therapist type	Description
Psychologist		Doctoral degree in psychology, counseling, or education
	Clinical and counseling psychologist	
	Licensed school psychologist	
Social Worker		Master's degree in social work
	Licensed clinical social worker	
	Licensed social worker	
	Licensed independent social worker	
	Academy of certified social worker	
Therapist or Counselor		Masters-level degree in psychology, counseling, marriage, or family therapy
	Licensed professional counselor	
	Creative arts therapist	
	Marriage and family therapists	
	Medical family therapist	
	Licensed clinical alcohol and drug abuse counselor	

basis [44]. Both family and professional caregivers make large sacrifices for loved ones with long-term chronic health condition. With caregiver burnout becoming a public health crisis [45], healthcare providers are often challenged to find resources to help offset the work demands of these individuals. Primary care providers should continue to check-in with caregivers during routine appointments with patients in practice.

Healthcare Team Approach

The physician is situated in a system of care that, when used, can greatly facilitate the care of conditions affecting the health of the patient. Integrative care, a key component of the patient-centered medical home, affords the physician access to expanded resources for assisting patients. Physicians who utilize healthcare professionals in their team can coordinate more effective services and care for patients and families [46]. In the area of coping with family stress, utilizing this team approach can offer additional resources to the patient and their family. There are many options for patients when working with a team. Below is a list of the most common therapist types available and brief descriptions from National Alliance of Mental Illness (Table 3) [47]. Each state has specific licensing requirements for therapists. Please see individual state licensing boards for requirements.

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Population-Based Health Care

5

Tanya E. Anim, George Rust, Cyneetha Strong, and Joedrecka S. Brown Speights

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Introduction

What Is Population Health?

The term "population health" is often attributed to David Kindig and Greg Stoddard, who defined it in 2003 as *"the health outcome of a group of individuals, including the distribution of such outcomes within the group."* Since then, definitions have expanded beyond a narrow focus on outcomes. Many definitions now connect health status and health outcomes to better healthcare and chronic disease management. Additionally, population health has also come to mean promoting health behavior change and addressing social determinants of health. Public Health and population health are closely linked but different. The

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Centers for Disease Control and Prevention (CDC) makes a distinction between public health and population health, noting public health's emphasis on primary prevention and infectious disease control. This is in contrast with population health, for which they quote George Washington University's Milken Institute – population health provides *"an opportunity for health care systems, agencies and organizations to work together in order to improve the health outcomes of the communities they serve* [1]." Public health focuses on ensuring conditions in which people can be healthy. Population health focuses on health outcomes and the determinants that influence those outcomes [2].

In practical terms, population health is the discipline of working to improve the health of groups of people rather than just individual patients. It takes different forms depending on the target population and the Family Physician's role. A state or county public health director is focused on prevention and other interventions to improve health outcomes across the entire population of a geographic area or jurisdiction. The discipline of community health focuses on neighborhoods or small communities, sometimes focusing on specific high-disparity populations. The managed care medical director may work through provider networks to influence health outcomes of hundreds of thousands of covered lives, while physicians in an Accountable Care Organization (ACO) may share financial risk for the health outcomes of thousands of patients attributed to their practice. At the individual Family Physician level, there is a panel of patients (often multiple panels connected to different payers) whose outcomes require intentional, team-based care management. However, population health from the Family Physician's perspective must take into consideration that which occurs beyond the four Walls of the office space, such as the influence of social, economic, political, and physical environments that affect the health of their patients and families [3].

Why Population Health?

US healthcare in the twenty-first century underperforms relative to the health systems of many other nations. Our costs are higher and our outcomes are worse. Meanwhile, there is increasing consumer demand for a better patient experience. In 2006, the Institute of Medicine's *Crossing the Quality Chasm* report presented six Aims for Improvement, calling for care that is safe, effective, patient-centered, timely, efficient, and equitable.

In 2006, John Whittington and Tom Nolan at the Institute for Healthcare Improvement (IHI) encouraged the move beyond care delivery to focus on outcomes, framed as the Triple Aim – (1) better health outcomes at (2) lower overall cost with (3) a higher quality of care defined from the patient's perspective, that is, a better experience of care for each patient. The Triple Aim concept was eventually woven into the Medicare program and into our national consciousness. In 2014, the Triple Aim was expanded to the Quadruple aim [4], adding wellness of the health care workforce and *"the joy of practice"* as an essential foundation for delivering high quality health care.

Taking these concepts to scale meant reorganizing practices and healthcare systems in order to demonstrate improvements across large groups of patients (practice panels and payer populations). It also meant changing the way providers would be paid, using all the financial force of the US Medicare program to actively promote a shift away from the volume-based, fee-for-service model to value-based models. CMS began promoting value-based models which would reward reductions in hospital admissions (starting with readmissions), emergency visits, and overall cost of care. Other health insurers and large self-insured corporations quickly followed suit. This also importantly meant that the wellness of the health care provider had to be incorporated into models of care that allowed for better efficiency of provider time, use of the electronic health record, tools to assist in quality delivery, promotion of resilience, and attentiveness to work-life balance.

Population Medicine

Individual Providers and Practices

At the level of the individual provider or practice group, the patient panel can be considered your "population" with regard to clinical outcomes and

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costs. For this reason, empanelment is a core element of population medicine at the primary care level. Empanelment is the act of assigning each patient to a primary care provider or team. Empanelment has the dual purpose of assigning responsibility between patient and a specific provider or team, but also establishing a denominator for measuring rates for quality, utilization, and outcome indicators. Effective care teams establish a long term provider-patient bond, continuity of care, and optimal, personalized care, in order to improve management and outcomes of chronic conditions, as well as providing evidence-based preventive care. Payers see this as a path to reducing costs by eliminating duplication of services and managing medical problems in the most appropriate setting. Physicians must know and track their panel size, keeping up with growth, attrition, and risk level, in order to assure that they have the resources necessary to meet the needs of their panel.

Defining the panel starts with identifying patients who have been seen in the practice within a certain time frame, such as within the past two years. The process is then refined with various inclusion or exclusion criteria. The spouse of a patient may identify him/herself as a patient of the practice, even if they have never had a visit, and the practice may choose to include them in their panel if so attributed by the payer. On the other hand, a practice may not want to include in their panel a patient who, for example, was seen once for a sprained ankle, missed several scheduled follow-up appointments, and has no intention of returning to the practice.

Defining the denominator population is essential for calculating outcomes such as hospitalization rates, emergency visit rates, and cost of care per thousand patients (often referred to by insurers as per thousand covered lives). Defining this population is also essential for building a pool for risk stratification and for monitoring outcomes and addressing needs of patients whether or not they choose to come for an office visit.

The team also must establish metrics of performance for managing their panel. Health care providers often prefer quality metrics over which they have a higher-level of control, such as the rate of performing in-office preventive services (e.g., Pap smears and flu shots). However, as the measures move from process to intermediate outcomes, such as rates of blood pressure or glycemic control, clinicians very quickly observe that they are being held accountable for metrics over which they only have partial control. While clinical inertia and the failure to intensify antihypertensive or diabetic regimens may trace back to clinician behaviors, patients are ultimately responsible for their own medication adherence, diet, and exercise. The responsibility and locus of control may shift even further from provider to patient when we consider utilization-based outcomes, such as hospital admissions, bed-days, re-admissions, emergency visits, and total health care costs per patient. Still, in a world of value-not-volume reimbursement, the clinician is responsible, if not financially at-risk, for managing these very outcomes. So, a core concept of outcomes-driven, panel-based care management is that while we cannot *control* patient behaviors or outcomes, we can *influence* those behaviors and outcomes. And while we cannot guarantee a good clinical outcome or lower costs for every individual patient, we can achieve predictably better results on group outcomes spread over a large enough panel of patients.

Chronic disease care management is another core element of the practice of population medicine, influenced strongly by Wagner's chronic care model (Fig. 1).

The foundation of the chronic care model is the dyad of an informed, activated patient and a prepared practice team. The model includes six functional elements: (1) self-management support, (2) delivery system design, (3) decision support, (4) clinical information systems, (5) organization of health care, and (6) community resources and policies [5].

Early iterations of care management were focused on single diseases rather than whole patients and started with disease registries. The paradigm of disease management shifted fairly rapidly to population health management when it became obvious that most patients did not have just one disease at a time. Patients in the diabetes registry often overlapped with those in the hypertension/cardiovascular disease registry, who also overlapped with those in the depression registry.

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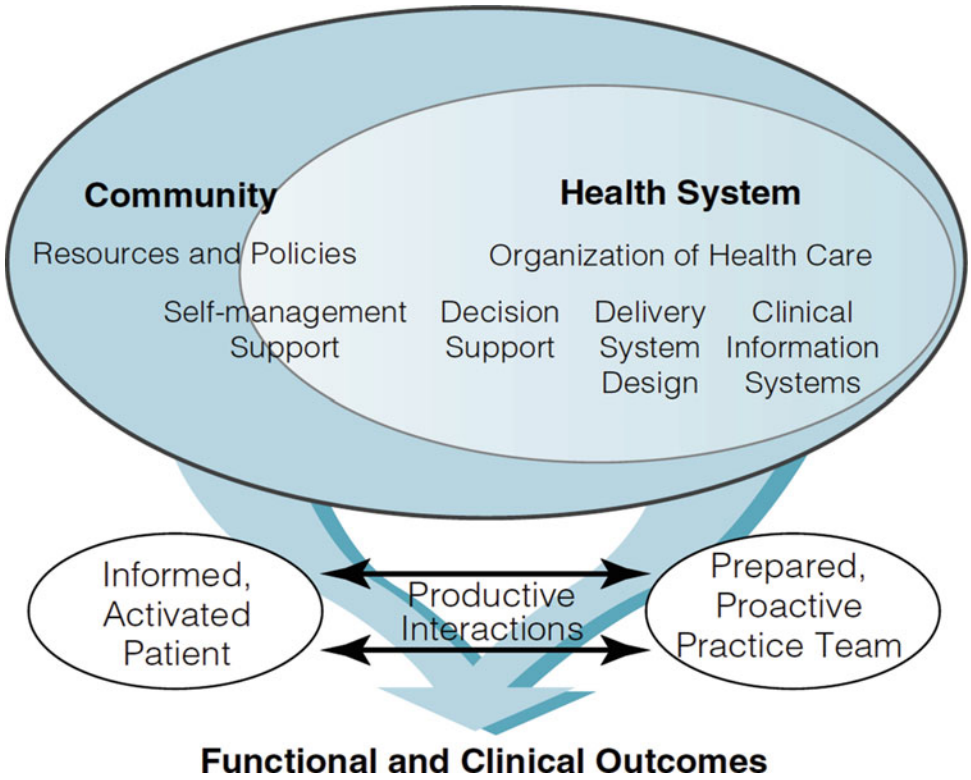


Fig. 1 Wagner [5]. (Used with permission)

In fact, the patients with multiple co-morbidities or multimorbidity turned out to be the patients who most needed to receive the on-going monitoring, care coordination, health education, patient navigation, medication reconciliation, and frequent follow-up contact that could improve clinical outcomes. Thus, disease management rapidly turned into care management at the practice level and into risk-stratified population health management at the levels of health systems and payers.

The core activities of patient empanelment and monitoring clinical metrics and care management are dependent on effectively using an electronic health record not just as a record of day-to-day patient care, but as a relational database that can be queried and produce actionable information in the care of individual patients as well as aggregate reporting on all patients or on subsets of the panel. This was the goal of the 2009 Health Information Technology for Economic and Clinical Health Act (HITECH Act) that mandated and incentivized adoption of electronic health records and established milestones of meaningful use. Querying the EHR data, producing aggregate reports, and creating real-time dashboards that track progress on clinical outcomes for the panel are additional competencies that will be required of every value-based primary care practice [6]. The key is to produce actionable information, to which the practice team can respond both for individual patients and for overall practice performance on panel-based outcomes. This requires dynamic interventions and the rapid-cycle feedback loops known in quality improvement circles as PDSA-cycles (plan-do-study-act).

In this century, primary care panel-based care management which is outcome driven is a team sport. Medical assistants are now engaging in expanded roles, including scribing and algorithm-driven preventive services. Registered nurses engage patients directly in care

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management, health coaching, and health system navigation. Psychologists, social workers, and licensed counselors can add capacity for full behavioral health integration in the practice. Peer counselors are increasingly recognized as having a powerful position on the healthcare team, with neighbor helping neighbor to achieve positive health behavior change and effective self-management. In multicultural settings, these may also be defined as community health workers or *promotoras*.

Some payers have begun specifically paying or rewarding primary care practices for "transforming" into patient-centered medical homes (PCMH). The concept of PCMH very much aligns with the principles of Population Health management. For more detail, please see ► Chap. 134, "Patient-Centered Medical Home".

All of these elements of population health management at the local practice level have been incorporated by Grumbach, Bodenheimer, and others into the comprehensive approach broadly described as *practice transformation*. The core building blocks of practice transformation are shown in Fig. 2 [7].

Population medicine becomes an essential part of a family physician's practice when the business model shifts from a fee-for-service practice to capitated or other value-based contracts. Simple primary care capitation fees pay the physician/practice a recurring payment per member per month (PMPM), regardless of whether or not the patient has a visit or receives other services. The practice takes on some financial risk in the sense that the cost of patient care in the practice must be covered by the monthly capitated revenue, but also gains tremendous freedom in building their team model to best focus on patient outcomes, rather than generating patient volumes. Care that can be managed by phone(telemedicine) or in group visits, for example, no longer requires that a billable service be provided in order to generate revenues.

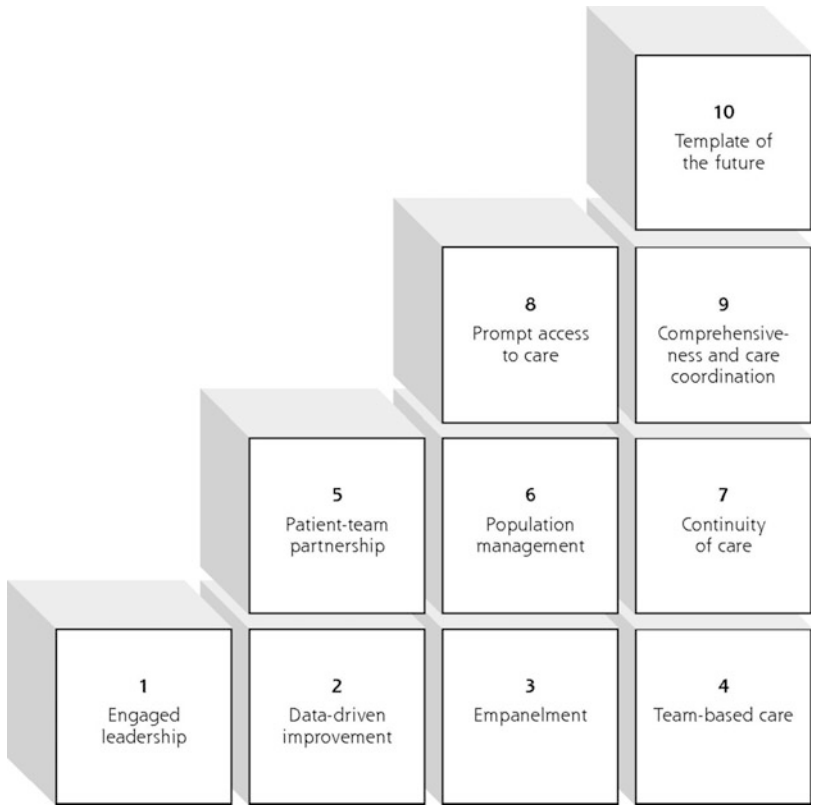


Fig. 2 Chronic Care Model, Brumbach, and Bodenheimer. The core building blocks of practice transformation. Bodenheimer et al. [7]. (Used with permission)

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This re-defines the business model of primary care and requires the primary care practice to know their own costs per empaneled patient rather than just knowing their own charges and collections minus costs per visit. In a sense, negotiating value-based payor contracts means that the practitioner must understand what drives the payer's costs and where the potential savings might come from improving patient outcomes.

Engaging in population medicine can have broad benefits for an entire patient panel and community. Increasing influenza vaccination rates in the practice through standing orders and patient reminders can decrease adverse clinical outcomes and increase "community immunity." At the same time, engaging in population medicine as a business model for primary care practice quickly draws attention to the 80–20 rule, that is, 20% of patients may generate up to 80% of the hospital bed-days and total cost of care. For this reason, payers engaged in population health management will use sophisticated "predictive analytics" to identify which patients are likely to be their high-cost high-utilizers and may seek to engage the primary care practitioner in more intensive care management of these patients. Patients risk-stratified as potentially high-utilizers may require "high touch" strategies to assure their healthcare needs are being met, even if they do not choose to come in for regular visits. Such patients may require various engagement or support strategies, such as emails, texts, or phone calls, weekly telehealth encounters, care navigation, home health services, mental health support, or even social work assistance with housing or transportation issues.

Population Health Management

Health Systems, Provider Networks, and Accountable Care Organizations

The continuum of population health blurs the boundaries between payers, networks, and providers. Increasingly, health care networks and hospital-based health systems engage in value-based care models, which create a distinctly different business model and care model than fee-for-service medicine. One example of population health management at the health system level is the Southcentral Foundation, an Alaska Native-owned, nonprofit health care organization. It emphasizes family-centered, relationship-based care for customer-owners who are at the center of all healthcare decision-making. They practice integrated behavioral and primary care in healthcare teams that also include culturally relevant native healers. The Southcentral system has demonstrated a rigorous ability to focus on outcomes and process measures in continuous data feedback loops to achieve transformational outcomes. A 40% drop in ER visits and a 36% drop in hospital stays represent not only less human suffering events, but also a strong impact on economic cost trends.

Hospital health systems and their network of affiliate physicians may now coalesce into accountable care organizations (ACOs), one form of what CMS refers to as advanced payment models. ACOs accept payments and enter into financial risk sharing agreements, initially with Medicare but often expanding into similar arrangements with Medicaid or with commercial payers. The formation of an ACO demands additional capacities including more sophisticated data management capabilities for feeding back outcomes such as emergency department visits to provider care management teams in real-time, alongside population health data management techniques including defining the denominator population (*attribution*), defining clinical and financial outcome metrics, understanding the utilization and cost variables that drive financial outcomes. Data are also needed on clinical risk factors and comorbidity profiles that drive adverse clinical outcomes (*predictive analytics*), and matching "touch levels" of how often and how frequently the practice calls, visits, or communicates with patients to their level of risk for adverse clinical outcomes, high utilization, and costs.

Predictive analytics not only allow for actuarial projections of utilization and financial risk, but also help to define risk stratification tiers and potentially preventable adverse outcomes. The aim is to determine the financial impact and

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resource utilization that a patient will have on the system.

There are a plethora of risk adjustment models that exist for this purpose [8]. In one study that compared the Acute Physiology and Chronic Health Evaluation, Sequential Organ Failure Assessment score, Charlson co-morbidity index, Model for End-Stage Liver Disease score and Simplified Acute Physiology Score (SAPS), SAPS appeared to perform best for predicting short term mortality. Otherwise, all of the methods seemed to perform similarly [9]. However, comorbidity scores created (and validated) for predicting in-hospital mortality are giving way to often-proprietary risk-scoring tools validated for predicting risk of hospitalization and/or total cost of care, such as the Ambulatory Care Grouper (ACG). Schneeweiss compared six approaches based on demographic and comorbidity profiles to find distinct differences in their accuracy regarding predicting utilization, and each of these methods was enhanced by adding data on numbers of prescribed medications [10].

To some extent, however, managing population health outcomes even at the ACO or health system level still depends on the power of the Family Physician and patient dyad, as well as the primary care team's effectiveness in helping its panel of patients to achieve optimal health outcomes. Combining this front-line connectedness with rapid-cycle data feedback loops that provide real-time information on patient utilization (emergency department visits, failure to refill needed medications, polypharmacy from seeing multiple providers, etc.) can enhance even further the effectiveness of the primary care team.

Population Health

Community Health and Social Determinants

Beyond population medicine or population health management, that is, the effort to manage healthcare delivery and health outcomes for groups of identified patients, is the broader notion of population health. While in population medicine or population health management, the population is typically defined by insurance payer source, health system, medical provider, or sometimes disease state (e.g., mental health carve-outs) [11], community health typically defines its population by geography (e.g., neighborhood or zip code) or by jurisdiction (parish or county) or by a vulnerable subset of a local population (e.g., homeless, migrant farmworkers) or by high-disparity racial sub-groups (e.g., the black or African American community). In the 1940s, two family physicians (Drs. Emily and Sidney Kark) began developing the conceptual framework of Community-Oriented Primary Care in partnership with communities, establishing more than 40 community health centers across South Africa. They describe their model in terms of "community medicine and primary health care as a unified practice," using the primary care practice as a base of operations, but focusing outward on the identification of community needs and the development of potential interventions in partnership with the community, followed by the implementation of interventions and re-assessment of targeted outcomes to dynamically improve the intervention with each iteration (Fig. 3) [12].

Ultimately, we seek to move beyond measuring disease-specific morbidity and mortality and to more generally assess the *health* of the community.

Population health cannot be assessed and fully addressed without taking into consideration the drivers and determinants of health outcomes, social determinants of health and health equity. Williams and others have framed this by saying that *"your zip code is more important than your genetic code in determining health outcomes."* The determinants of health are the conditions in which people live, work, move, breathe, and play that influence overall health. Environment significantly contributes to each individual's health not just at one moment in time, but in all places (whether physical, mental, emotional, social, spiritual, financial, or intellectual) with which one interacts in their socioeconomic and cultural contexts over time.

Many factors impact the health of populations over the course of life. Factors at the individual,

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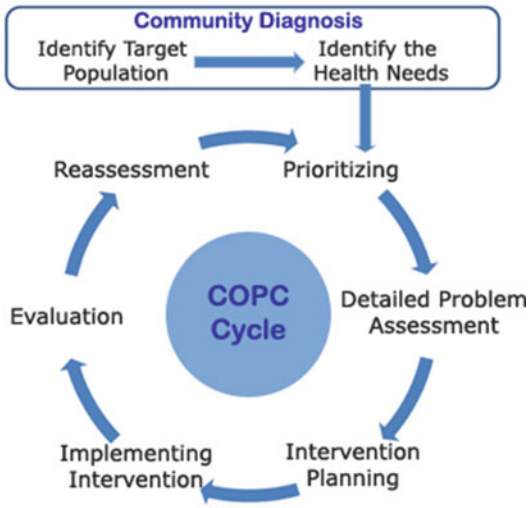


Fig. 3 Community-oriented primary care Model. Integrating Primary Care and Public Health: Learning for the Community-oriented Primary Care Model [12]. (The figure derived from the original version published in 2003 was created by Dr. Joo et al. at Columbia university. Primary Care Online Resources and Education. Prevention – Community Oriented Primary Care [Internet]. Columbia NY: Columbia University [cited 2020 July 11]. Available from: PCORE website. Used with permission)

family, community, systems, and policy level create environments that promote healthy lifestyles and facilitate access to nutritious food, clean water, clean air; primary care including preventive services and behavioral health; quality education from early childhood; good jobs with fair pay; and minimize toxic stress, discrimination, and racism. The opposite is quite true – that if someone is exposed to unhealthy living spaces, stressors early on and over time, that individual is more likely to carry a substantial allostatic load that is associated with endovascular and neurohormonal pathology. They may also be more likely to engage in health risk behaviors, and experience poor health choices early in life with subsequent increased risk of chronic diseases, mental health problems, and premature death [13].

Family physicians recognize that health as not merely the absence of disease, but as wholeness in multiple domains, such that people and communities have the opportunity to live well and thrive. The practice of population medicine and population health calls us to return to a commitment to treating patients in the context of family and community.

The complex causation of health behaviors, health disparities, and adverse health outcomes at the community level requires multidimensional interventions to achieve even simple outcomes. For example, improving rates of initiation of breastfeeding in a community might start with creating a culture of normalization and encouragement of breastfeeding in the workplace and other public areas, offering private areas to breastfeed that are well publicized and accessible, and providing an area to pump and store milk in the workplace. Family physicians can be leaders in incorporating these elements into their practices, while also offering brief breastfeeding education to every pregnant patient at each prenatal visit. At a community level, breastfeeding coaches can be trained and supported, faith communities can provide both messaging and social support, and media (both traditional and social media) can be engaged in broader public campaigns.

To be effective in achieving collective impact requires a re-thinking of our practice role, as well as a new understanding of our communities. Too often, high-disparity neighborhoods have been characterized by deficits or needs-assessments, including degrading terms such as poverty, deprivation-index, or broken-windows index. Community health development models such as asset-based community development (ABCD) require a balanced approach that also sees the strengths and resiliency of communities and works to inventory and build on their resources and assets. This is not work that can be done at a distance. It is foundationally built on trust-based relationships with members of the community who also have trust-based relationships with other members of the community. The person who claims to be a community leader may not indeed "speak for the community." Only relational trust developed over years will be effective across the diversity and within-group heterogeneity that is characteristic of community populations.

Community health centers (CHCs), migrant health centers, and federally qualified health centers (FQHCs) are community-led organizations

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which receive federal grant funding from the Health Resources and Services Administration (DHHS/HRSA). While many serve primarily as a comprehensive, culturally relevant healthcare delivery system for uninsured and underserved patient populations, their origins were in community health development for the purpose of transforming the health of communities themselves.

Public Health

Public health can be defined broadly as all the "public, private, and voluntary **entities**" working together to achieve health of the public in a geographically (or jurisdictionally) defined population. The dependence on an interconnected web of agencies and stakeholders is illustrated in Fig. 4 [14].

However, a subset of public health is a set of highly structured activities conducted through formally defined agencies at various levels from county or parish health departments and state health departments, which are in turn connected with federal activities such as the Centers for Disease Control and Prevention.

While these agencies may differ substantially from one community to another in structure and in the extent to which they provide direct services (versus "assuring" that services are being offered in the community), their role has been summarized in these ten essential functions of public health (Fig. 5) [14].

Some health departments offer primary care, although less so in recent years. More often, direct patient care may be provided in categorical services, tied to specific lines of state or federal funding. These might include family planning and immunization programs, for example.

Public health departments also have a specific focus on communicable diseases – treating and tracking individuals with some historically high-impact infectious diseases such as tuberculosis and syphilis to protect the public. When new conditions emerge, as did HIV/AIDS in the 1980s, or COVID-19 in 2020, public health agencies are on the front lines of identifying cases, surveilling for outbreaks, tracing contacts, and

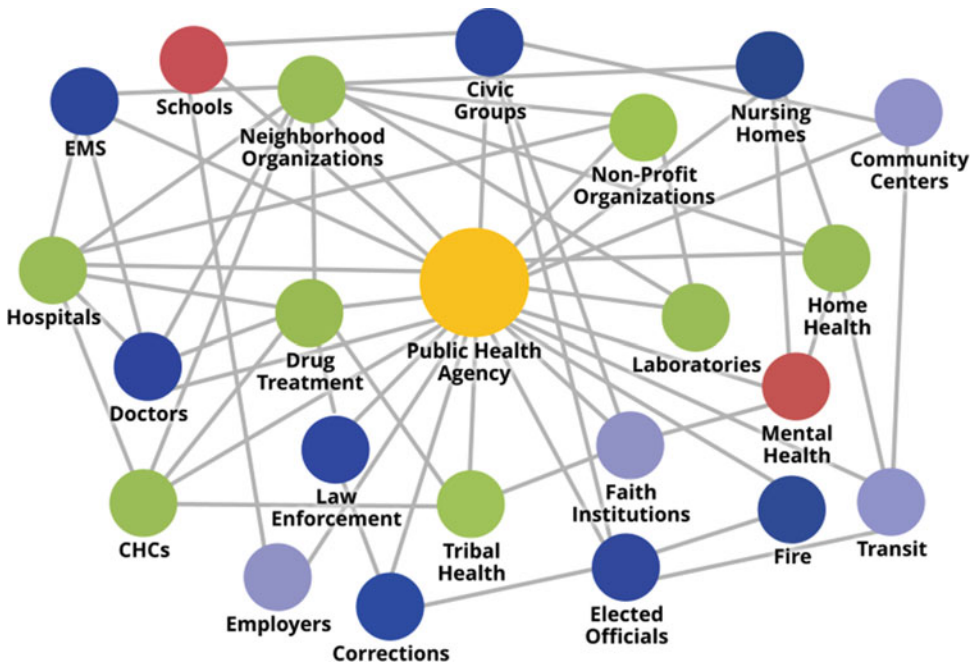


Fig. 4 The dependence on an interconnected web of agencies and stakeholders (CDC). Centers for Disease Control [14]. (Used with permission)

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Fig. 5 The 10 Essential Public Health Services. Centers for Disease Control [14]. (Used with permission)

even enforcing isolation for infected patients or quarantine for those exposed.

Public health may be contrasted with population health management by its focus on primary prevention, in areas such as encouraging healthy lifestyle, diet, and exercise. They may specifically engage in obesity prevention, tobacco programs, HIV prevention, and community health education. Public health may also focus on key health status indicators, such as infant mortality, and may direct specific attention to disparities in outcomes. The black-white infant mortality gap, for example, can be measured for public awareness and the development and assessment of interventions by broader community coalitions. This primary prevention focus contrasts with managed care population medicine, which tends to focus on secondary and tertiary prevention for persons with significant health issues and multimorbidity.

Health Policy

It is easy to see the direct connection between the health of the US population and health policy interventions such as the Affordable Care Act (ACA), or the state-level decisions to expand (or not expand) Medicaid coverage to all persons with incomes below 138% of the federal poverty level. Not only did the ACA expand affordable

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health insurance coverage to millions of Americans, it expanded on previous legislation such as the Mental Health Parity Act of 1996 (MHPA), which provided that large group health plans could not impose limits on mental health benefits any greater than those imposed on medical/surgical benefits. This was further extended by the Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA) to cover substance abuse treatment parity.

In the prevention realm, initiatives such as the Vaccines for Children program have an obvious connection to health, but safety legislation such as the 1966 National Traffic and Motor Vehicle Safety Act and the related Highway Safety Act have also had a major health impact, reducing automobile-related fatality rates (which by 1965 had become the leading cause of death for adults under age 40) by over 50%.

Further, our increasing awareness of the social determinants of health leads to a much broader understanding of how policy and legislation can drive health outcomes. Both state and federal policies related to crime and the "war on drugs" led to mass incarceration, disproportionately affecting persons of color despite relative equality in actual use of drugs across racial-ethnic groups. Having a prison record dramatically affects employability and long-term economic opportunities, which are directly tied to a person's opportunity to achieve and maintain optimal health. Homelessness has a profound effect on health, leading some communities to adopt a "housing first" approach to helping the homeless and others to seek larger-scale solutions to affordable housing.

Structural, institutional racism affects individuals in such diverse ways as harsh inequality of public schools across racially defined neighborhoods, which often followed from residential segregation and the redlining of neighborhoods, which is tied to the profound racial wealth gap that far exceeds the more well-publicized problem of income inequality. Examples abound –neighborhoods of color are often centered in food deserts, and food insecurity is closely associated with long-term obesity. Toxic waste sites are geographically situated in low-income communities, as are point sources of industrial air pollution, giving rise to an entire field of advocacy known as environmental justice.

At local and state levels, this understanding has led to a demand for "health in all" policies, starting with a requirement that health impact assessments be undertaken for any new development or project, whether a new highway or new business construction, or new crime legislation. A health-in-all approach to the effects of incarceration as a societal means for addressing issues of substance abuse or mental illness might lead to more aggressive efforts at diversion such as mental health courts or drug courts, as well as an increased devotion of resources to child mental health services as an alternative to the juvenile justice system.

Family Physicians often have the ideal combination of training, knowledge, experience, and front-line observations to be effective advocates for "health-in-all" policies in their own community, as well as at the state and national levels. Discipline is required to advocate for and with members of our community on behalf of our patients, rather than on behalf of our profession.

Even as this chapter is being written, a worldwide pandemic of the novel Coronavirus designated as COVID-19 is overwhelming healthcare delivery systems and dramatically impacting population health outcomes (morbidity and mortality) across the United States and across the world. In this moment, we begin to understand that the health of all people in our nation and in our world is *our* health. We are all interconnected. Individual health outcomes not only add up to aggregated population health indicators, but population health factors can affect our own individual health.

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Part II

Preventive Care

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Clinical Prevention

6

Roger J. Zoorob, Maria C. Mejia, and Robert S. Levine

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Traditionally, there are three tiers of clinical prevention: (a) primary, before disease onset; (b) secondary, after disease onset but before clinical signs or symptoms; and (c) tertiary, after clinical signs and/or symptoms. Examples include immunization (primary), screening (secondary), and post-diagnostic patient education (tertiary, e.g., teaching patients with pedal peripheral neuropathy to check bathwater temperatures with their arms).

Healthy People 2020 Leading Health Indicators

The Healthy People program, led by the US Centers for Disease Control and Prevention (CDC), provides a national blueprint for health that identifies 26 objectives to communicate high-priority issues, four of which apply directly to clinical prevention. Improvement has been mixed: colorectal cancer screening increased from to 59% in 2010 to 65% in 2018, with a target of 71% by 2020 [1], and for childhood immunization, the percentage of children receiving recommended doses of DtaP, polio, MMR, HiB, hepatitis, varicella, and PCV vaccines by ages 19–35 months increased from 68% in 2012 to 70% in 2017 with a target of 80% by 2020 [2]. However, the percentage of adults with hypertension whose blood pressure is under control decreased from 49% in 2009–2012 to 48% in 2013–2016, with a target of 61% by 2020 [3], and diabetes control decreased from 21% in 2008–2012 to 19% in 2013–2016 [4]. More encouraging, 47% of adults ages 50–64 and 68% of adults 65 and older received influenza immunizations in 2018–2019 an increase of 7.1% and 8.5%, respectively, as compared to 2017–2018 [5].

Screening Evidence in Clinical Prevention

Screening is the most prominent example of secondary prevention. In general, screening is appropriate when the following conditions are met: (a) the disease must affect a sizable portion of the population and/or have a high level of severity; (b) the detectable preclinical phase of the disease cannot be so short as to require rapid re-screening since this can become overwhelming in terms of logistics and/or cost; (c) early detection must lead to either a better outcome for the individual being screened or effective prevention of the spread of the disease to others, and these benefits must be more likely when the disease is detected before signs or symptoms appear; and (d) the screening test itself must be safe, acceptable to those targeted for screening, and valid (i.e., sufficiently capable of truly distinguishing between those with and without the disease) [6]. Further, when evaluating a screening program, several types of bias must be avoided. These include lead time bias (e.g., crediting early detection with improved survival when all that has happened is earlier detection); prognostic selection bias (people who choose to be screened may be more likely to take care of themselves and therefore to have a better clinical course than those who do not choose to be screened); and length bias (deaths due to more aggressive disease may occur during the inter-screening interval, meaning that disease detected at screening is less severe) [7]. Randomized, controlled trials are ways to overcome such bias [7].

A number of measurements are available for assessing screening tests. An example is shown in Fig. 1 (a), screening test positive and disease present (true positives), 300; (b), screening test positive and disease absent (false positives), 100;

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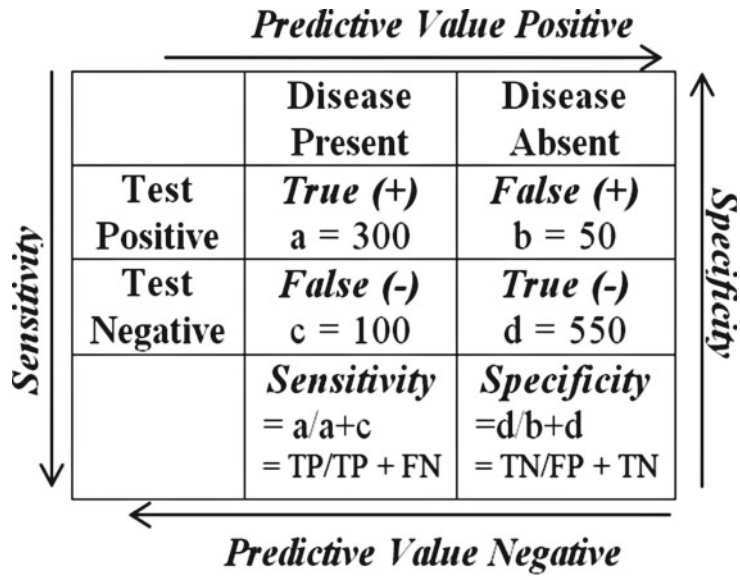


Fig. 1 Sensitivity and specificity of screening tests

As the cutoff criterion decreases, the number of false (-) decrease while false (+) increase, thereby increasing sensitivity and decreasing specificity. In contrast, as the cutoff criterion increases, the number of false positives decrease and the number of false negatives increase, thereby increasing specificity and decreasing sensitivity.

(c), screening test negative and disease present (false negatives), 50; and (d), screening test negative and disease absent (true negatives), 550. In this case, sensitivity, or positivity in disease, is 300/350 or 86%. Tests with high sensitivity have relatively few false-negative results. Specificity, or negativity in health, is 550/650 or 85%. Tests with high specificity have relatively few false-positive results.

While some screening test results are dichotomous ("yes" or "no," as for tuberculin skin tests), many others, such as fasting plasma glucose, are continuous. When screening results are continuous, a cutoff value is often chosen to distinguish a positive test from a negative test. This produces a trade-off between sensitivity and specificity. Specifically, as the cutoff criterion decreases, the number of false negatives decreases, while that of false positives increases, thereby increasing sensitivity and decreasing specificity. In contrast, as the cutoff criterion increases, the number of false positives decreases, and the number of false negatives increases, thereby increasing specificity and decreasing sensitivity. Also, the specificity of a test may be improved (and sensitivity reduced) by requiring a positive result from two tests, while the reverse occurs if a positive result on either of two tests is required. Receiver operating characteristic (ROC) curves – graphs in which sensitivity (y-axis) is plotted against 1-specificity (x-axis) – are also used to estimate the best cut point.

Several other types of information may be obtained. These include:

- Prevalence = (a + c)/(a + b + c + d) = 350/1000 = 35% = proportion of persons being tested who have the disease.
- Accuracy = (a + d)/(a + b + c + d) = 850/1000 = 85%. If the prevalence of the disease being tested differs in two populations

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undergoing screening, the accuracy of the test could be different even if the sensitivity and specificity were the same.

- Predictive value of a positive test (PV+) = a/a + b = 300/400 = 75% = proportion of persons with a positive screening test who have the disease. As the prevalence of disease among those being screened decreases, the PV+ decreases.
- Predictive value of a negative test (PV−) = d/c + d = 550/600 = 92% = proportion of persons with a negative screening test who do not have the disease. As the prevalence of the disease among those being screened decreases, the PV− increases.

PV+ and PV− are both influenced by prevalence. For example, screening for a hematologic disease in a hematologist's office would be expected to produce a higher predictive value than screening with the same test in a primary care clinic. Positive and negative likelihood ratios, in contrast, address similar questions but do not depend on prevalence:

- Positive likelihood ratio = sensitivity/(1-specificity) = 0.86/0.15 = 5.73 = a positive screening test is 5.73 times more likely to occur among those with the disease than among those without the disease.
- Negative likelihood ratio = (1-sensitivity)/specificity = 0.14/0.85 = 0.16 = a negative screening test is 0.16 times more likely among persons with the disease than among persons without the disease.

In all cases, the discomforts and risks associated with screening, including the stress of waiting for diagnostic results and possible adverse effects associated with testing, need to be considered when ordering a screening test.

Health Maintenance

All clinical encounters are opportunities for health promotion and disease prevention, including early identification of risk behaviors and disease, updating immunizations, and providing health guidance. Family medicine encounters, in turn, act in conjunction with preventive interventions provided through schools and other community resources. The United States Preventive Services Task Force (USPSTF) is a leader in providing evidence-based guidance for clinical prevention in primary care. The Task Force is an independent volunteer panel made up of experts from preventive and primary care medicine and nursing. Convened by the Agency for Healthcare Research and Quality (AHRQ), the Task Force gives a letter grade based on the strength of evidence pertaining to the benefits and harms of services that may be offered to people being in the primary care setting and who do not have signs or symptoms of a specific disease or condition. "A" and "B" grades are given to those services for which the Task Force has found good or fair evidence of benefit. As of this writing, preventive services which are generally covered by insurance may be identified at URL: https://www.healthcare.gov/coverage/preventive-care-benefits/. The Task Force does not review all types of preventive services, however. In particular, it defers to the Advisory Committee on Immunization Practices (ACIP) for reviews and updates of the recommended immunization schedule, and it refers users to the Health Resources and Services Administration (HRSA) Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) for recommendations on screening for heritable diseases in newborns. Primary care physicians should refer to the CDC Vaccines and Immunizations website (http://www.cdc.gov/vaccines/recs/default.htm) for updates and the most current schedules and to the website of the Advisory Committee on Heritable Disorders in Newborns and Children (https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html) for information that is up to date as of the end of Congressional statutory authorization for this committee in September 2019. In the following sections, primary and secondary preventive services as recommended by the Task Force and other organizations according to patient age are described. Additional reviews of prevention for infectious diseases (e.g., post-exposure, travel and occupational prophylaxis, screening for tuberculosis,

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etc.) may be found in other chapters in this volume.

Key Recommendations from the US Preventive Services Task Force (USPSTF) and Advisory Committee on Immunization Practices (ACIP)

Estimates of highest priority in terms of scoring for quality-adjusted life years (QALYs) that could be gained if the clinical preventive service was delivered as recommended (five point maximum) and cost-effectiveness (five point maximum) were the ACIP childhood immunization series (10 points); interventions to prevent initiation of tobacco use including education or brief counseling (10 points); and tobacco use screening, brief cessation counseling, and pharmacotherapy (10 points) [8]. Also scoring highly (eight points) were cervical cancer screening for women ages 21–65 with cytology, colorectal cancer screening of adults ages 50–75 years, and screening and counseling for alcohol misuse [8]. As of 2016, the USPSTF recommended low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer among adults aged 50–59 years who have a 10% or greater 10-year cardiovascular disease risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years [9]. In 2019, the American College of Cardiology and the American Heart Association noted that people between 40 and 70 years of age at high risk of cardiovascular disease (a strong family history of heart attack and uncontrolled blood pressure, cholesterol, or diabetes) and a low risk of bleeding may benefit from low-dose aspirin in addition to those who have a history of heart attack, stroke, coronary stent, or coronary artery bypass surgery and are at low risk of bleeding. In contrast, aspirin was not recommended for healthy people over 70 or under 40 years of age or for people at increased risk of bleeding because of a medical condition or other medication. A healthy diet, exercising, not smoking, and controlling high cholesterol, high blood pressure, and diabetes are among preventive steps to be taken beyond aspirin [10]. USPSTF and ACIP recommendations are constantly evolving and may be accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/home and https://www.cdc.gov/vaccines/acip/recommendations.html, respectively.

Prevention for Infants, Children, and Adolescents (Birth to 18 Years)

Immunization

Birth to 18 Years: The immunization program is one of the most successful examples of effective preventive care in the United States. Through immunization, infants and children can be protected from at least 14 vaccine-preventable diseases before age 2. Low prevalence of most vaccine-preventable diseases has been the result of high coverage (90% and above) for many childhood vaccinations in the last two decades. Yet, while coverage has remained high and stable overall (more than 90% of children ages 19–35 months are getting the recommended vaccines), booster shots and second doses lag for 2-year-olds [11]. Additional efforts by parents and healthcare providers are warranted to maintain and improve the rate of administration of recommended immunizations.

The ACIP recommends the administration of all age-appropriate vaccines during a single visit. If a dose is not administered at the recommended age, however, it should be administered at a subsequent visit. The CDC Vaccines and Immunization website provides the catch-up schedule. The Childhood Vaccine Assessment Tool is also available at https://www2a.cdc.gov/vaccines/childquiz/. Through this link, providers can generate a personal, customized patient immunization schedule.

In addition to *childhood immunizations*, ACIP recommends that *immunizations for adolescents* include one dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine; two doses of meningococcal conjugate (MenACWY) vaccine; and three doses of human papillomavirus (HPV) vaccine [12]. Annual

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influenza for all persons aged ≥6 months and "catch-up" vaccinations, such as measles, mumps, and rubella (MMR), hepatitis B, and varicella, are also recommended [12]. See Fig. 2.

Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/. For information regarding vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.

Federal law mandates that healthcare staff provide a Vaccine Information Statement (VIS) containing both the benefits and risks of a vaccine to a patient, parent, or legal representative prior to the administration of a vaccine. Adverse events associated with vaccines should be reported to the DHHS using the Vaccine Adverse Event Reporting System (VAERS, http://vaers.hhs.gov/index).

Prophylaxis

Newborn: At present, 0.5% erythromycin ophthalmic ointment is the only approved drug for *ocular prophylaxis for gonococcal ophthalmia*

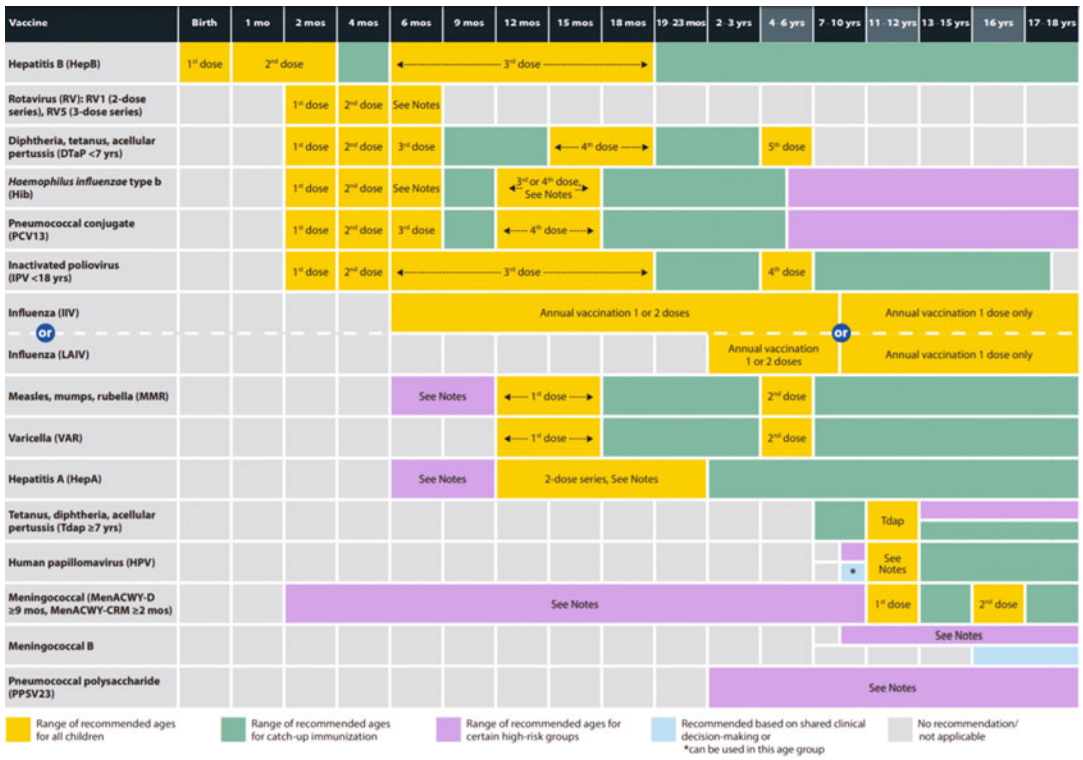


Fig. 2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2020. Note: The above recommendations must be read along with the footnotes of this schedule. See https://www.cdc.gov/vaccines/schedules/downloads/child/0–18years-child-combined-schedule.pdf. This schedule includes recommendations in effect as of January 1, 2020. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. School entry and adolescent vaccine age groups are shaded in gray. Always make recommendations by determining needed vaccines based on age; determining appropriate intervals for catch-up, if needed; assessing for medical indications; and reviewing special situations. Administer recommended vaccines if immunization history is incomplete or unknown. Do not restart or add doses to vaccine series for extended intervals between doses. When a vaccine is not administered at the recommended age, administer at a subsequent visit. Vaccination providers should consult the relevant ACIP statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html. Clinically significant adverse events that follow vaccination should be reported to the VAERS online (http://www.vaers.hhs.gov).

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neonatorum by the US Food and Drug Administration (FDA). The USPSTF recommends this for all newborns, while the pediatric Red Book states it should be given when gonorrhea is prevalent in the region and prenatal treatment cannot be ensured or where required by law. The Red Book also cautions that efficacy is unlikely to be influenced by a delay of 1 h to facilitate parental bonding but that longer delays have not been studied for efficacy [13].

6 Months to 17 Years: For oral health, the USPSTF recommends applying *fluoride* varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption and prescribing oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride (<0.6 mg fluoride ion/L [ppm F]). Pediatric sources including the AAP Section on Oral Health add that the fluoride varnish should be repeated every 3–6 months. For high-risk children, an over-the-counter fluoridated mouth wash is recommended starting at 6 years of age if the child can reliably swish and spit. High risk is determined by both maternal/caregiver factors (mother or caregiver who does not have a dentist or who has had active decay in past 12 months) and child attributes (continual bottle/sippy cup use with fluid other than water; frequent snacking; special healthcare needs; and Medicaid eligible) [14].

Counseling and Anticipatory Guidance

Prenatal

Folic acid prophylaxis (400–800 micrograms per day) is recommended for all women who are planning or capable of pregnancy in order to prevent neural tube defects (Table 3).

Birth to 2 Years: This part of the visit allows the family physician to provide culturally and developmentally appropriate information about the patient and is an effective tool to educate parents about maintaining children's health. It is also important to document all counseling efforts. Particular attention should be given to parental concerns such as those related to newborn care, breastfeeding decisions, potential health/environmental risks, and safety. *Breastfeeding* should be encouraged. The benefits of breastfeeding include lower risk of acute otitis media, asthma, eczema, atopic dermatitis, and gastrointestinal tract infection, sudden infant death syndrome, and chronic conditions such as obesity, diabetes, and high blood pressure. The AAP recommends exclusive breastfeeding and/or human milk for infants for the first 6 months of life and continuing at least through the first year in addition to complementary foods, except in rare circumstances such as maternal contraindications or galactosemia. The USPSTF found adequate evidence to indicate that formal breastfeeding education increases rates of initiation, duration, and exclusivity of breastfeeding. Although the USPSTF has not made a recommendation about infant *safe sleep*, sudden infant death syndrome (SIDS) incidence has decreased since the AAP's 1992 recommendation that infants be placed for sleep in a non-prone position. However, recent data show an increase of other causes of sleep-related deaths including suffocation, asphyxia, and entrapment. To address this new evidence, the guidelines have been updated to 19 recommendations for a safe sleep environment for all infants, including back sleeping (supine), a firm sleep surface, breastfeeding, room-sharing without bed-sharing, and avoidance of overheating and exposure to tobacco smoke, alcohol, and illicit drugs [15]. Children are particularly vulnerable to the effects of *secondhand smoke*. It increases the risk for SIDS, asthma, otitis media, and lower respiratory tract infections [16]. The AAFP offers the following recommendations on protecting children from tobacco, nicotine, and tobacco smoke, all of which apply, directly or indirectly, to secondhand smoke:

1. Inquire about tobacco use and tobacco smoke exposure as part of health supervision visits and visits for diseases that may be caused or exacerbated by tobacco smoke exposure.
2. Include tobacco use prevention as part of anticipatory guidance.
3. Address parent/caregiver tobacco dependence as part of pediatric healthcare. (3a) Recommend tobacco dependence treatment of tobacco-dependent parents and caregivers. (3b)

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Implement systems to identify and offer counseling, treatment, treatment recommendations, and/or referral for tobacco-dependent parents.
4. Offer tobacco dependence treatment and/or referral to adolescents who want to stop smoking. (4a) Tobacco dependence pharmacotherapy can be considered for moderate to severely tobacco-dependent adolescents who want to stop smoking.
5. Offer tobacco-dependent individuals quitline referral.
6. Consider potential for neuropsychiatric symptoms with tobacco dependence treatment.
7. Do not recommend electronic nicotine delivery systems for tobacco dependence treatment.
8. If the sources of a child's tobacco smoke exposure cannot be eliminated, provide counseling about strategies to reduce the child's tobacco smoke exposure [17].

Primary prevention with provider counseling to include screening via environmental risk assessments for lead exposure is recommended at 6, 9, 12, 18, 24, and 30 months and at 3, 4, 5, and 6 years of age according the current Bright Futures/Periodicity Schedule, with blood lead level testing to occur if the screen is positive and/or if the child lives in a high prevalence area (e.g., children who are on Medicaid, living in poverty, and living in older housing are considered to be at especially high risk [USPSTF Grade I]). Capillary blood testing should be confirmed by venous blood testing. The physician should inquire about in-home exposures, unsafe renovation practices (houses built before 1978), and potential lead exposures associated with parental occupations and hobbies. Further, the American Academy of Pediatrics (AAP) has stated that, "Evidence continues to accrue that commonly encountered blood lead concentrations, even those below 5 μg/dL (50 ppb), impair cognition; there is no identified threshold or safe level of lead in blood." Evidence-based guidance is available for managing increased lead exposure in children, and reducing sources of lead in the environment, including lead in housing, soil, water, and consumer products, has been shown to be cost-beneficial. Primary prevention should be the focus of policy on childhood lead toxicity [18].

The AAP issues extensive policy statements on the prevention of *drowning*, including 40 recommendations and resources for parents and caregivers and pediatricians [19]. Recommendations have also been issued for exposure to digital media in 2–5-year-olds (summarized in the following section).

3 to 10 Years: Anticipatory guidance and counseling for *lead exposure* should continue through at least 5 years of age. Anticipatory guidance is also warranted during well-child visits in such areas as nutrition, healthy lifestyle practices, and injury prevention. Recommendations for counseling for *lifestyle risk factors* include encouraging a diet high in fruits and vegetables and low in fats; eating a healthy breakfast daily; regularly eating meals as a family; limiting the consumption of sweetened beverages, fast foods, and high-fat snacks; and limiting digital media use (including television). Evidence is sufficient to recommend time limitations on digital media use for children 2–5 years to no more than 1 h per day to allow children ample time to engage in other activities important to their health and development and to establish media viewing habits associated with lower risk of obesity later in life. It is recommended that children below the age of 2 years should not have any exposure to digital media [20]. Personalized plans need to be developed for older children and adolescents. Several recommendations are made, including the need for consistent limits; need to assure time for at least 1 h of physical activity and 12 h of sleep per day; awareness of cyberbullying and cybersexting; awareness that exposure of adolescents through media to alcohol, tobacco use, or sexual behaviors is associated with earlier initiation of these behaviors, in part because peer viewers may see adolescent displays of substance use, sexual behaviors, self-injury, or disordered eating as normative; and awareness that research from both the United States and United Kingdom indicate that major alcohol brands maintain strong presences on Facebook, Twitter, and YouTube [21]. Parents should be encouraged to motivate their children to

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play and to lead by example by participating in an active lifestyle.

Drowning is the main cause of death due to injury among children aged 3–4 years, and anticipatory guidance is important throughout childhood and adolescence [19]. Most deaths of children ages 5–10 years are due to *traffic injuries*, as occupants, pedestrians, bicyclists, or motorcyclists. The USPSTF refers clinicians to the CDC's Community Guide recommendations for actions that they could support within the community, such as laws mandating the use of children's car seats, safety belts, and helmets along with education programs, community-wide information, and enhanced enforcement campaigns (http://www.thecommunityguide.org). The use of child safety seats and safety belts is among the most important preventive measures to reduce motor vehicle-related injuries and deaths. The AAP formerly recommended that infants and toddlers should ride in a rear-facing car seat until they are at least 2 years old, but updated recommendations eliminate the age milestone, offering five recommendations: (1) rear-facing car safety seats as long as possible; (2) forward-facing car safety seats from the time children outgrow rear-facing seats, for most children through at least 4 years of age; (3) belt-positioning booster seats from the time children outgrow forward-facing seats, for most children through at least 8 years of age, and lap and shoulder seat belts for all who have outgrown booster seats; and (5) for all children younger than 13 years to ride in the rear seats of vehicles. The AAP recognizes that every transition is associated with some decrease in protection; therefore, parents should be encouraged to delay these transitions for as long as possible [22].

11 to 18 Years: *Unintentional injuries* (from traffic injuries and other causes as stated above) continue to be major causes of death, and counseling/anticipatory guidance should continue as well. Counseling and interventions to reduce *cardiovascular risk* (e.g., healthy weight, smoking cessation) and reduce involvement in health risk behaviors (e.g., alcohol and drug use, unsafe sexual practices) are also a priority. Anticipatory guidance should be provided about the benefits of regular physical activity (at least 60 min per day) to reduce the risk of developing obesity and chronic diseases, decrease the risk of depression and anxiety, and promote psychological well-being. Children age 10 years and above who have fair skin should be advised about minimizing their exposure to ultraviolet radiation to reduce risk for skin cancer and especially to avoid excess/midday sun exposure, wear protective clothing, and use sunscreen as directed.

Parents should be encouraged to lead by example by providing a healthful food environment and by discouraging the consumption of unhealthy foods outside the home. Family dinners could benefit teens' mental health by creating a conducive environments for open communication between parents and children to mitigate risks of *cyberbullying* and other online challenges [23]. Promoting the healthy and safe use of social media could prevent associated *mental health* and *substance use* problems as well as other risks related to technology use itself (e.g., distraction or sleep problems) in children and adolescents [23]. In addition to counseling about avoiding online behaviors that can have negative consequences, such as "sexting" and sharing of personal information and pictures with strangers, the clinician should confer about strategies to deal with bullying and resources such as creating a *personalized family media use plan* available through recognized organizations such as Bright Futures (https://www.healthychildren.org/English/media/Pages/default.aspx#home).

Sexual risk behaviors among adolescents increase the risk of unintended pregnancy and *sexually transmitted infections* including *HIV.* Young people aged 13–24 accounted for an estimated 21% of all new HIV diagnoses in the United States, and they are the least likely of any age group to be linked to care in a timely manner and have a suppressed viral load [24].

Driven by an increase in e-cigarette use, current tobacco product use has significantly increased among high school and middle school students, hindering the decline in tobacco product use among youths that occurred in previous years. Education and counseling reduce the chances children and teens will start smoking. Interventions include direct counseling with teens individually

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or with families, videos, apps, print materials, activity guides, workbooks, and preprinted prescriptions. While there is insufficient evidence that routine counseling by an individual practitioner to reduce *alcohol* and *illicit drug misuse* in children and adolescents is effective, the AAFP recognizes the importance of counseling aimed at alcohol avoidance by adolescents aged 12–17 years and strict prohibition of driving under the influence of alcohol or impairing agents at any age.

Screening

Comparisons between USPSTF and the American Academy of Pediatrics (AAP) screening recommendations are summarized in Tables 1 and 2.

Newborn: Certain *genetic, endocrine, and metabolic disorders*, as well as *hearing loss* and critical *congenital heart disease* (CCHD), can adversely affect an infant's survival or inhibit a child from achieving full potential. It has been 50 years since the US newborn screening program was first implemented. Universal newborn blood screening *for phenylketonuria (PKU)*, *congenital hypothyroidism (CH)*, and *sickle cell disease* is now mandated in all 50 states. Although State law determines which disorders are included in the screening, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) recommends that states test for a *core panel of 35 congenital disorders and 26 secondary disorders*, including severe combined immunodeficiency (SCID) [25]. The USPSTF recommends that infants who are tested for *PKU* within the first 24 hours after birth should receive a repeat screening test by 2 weeks of age. Screening for *CH* should be done between 2 and 4 days of age or immediately before discharge if this occurs earlier. Confirmatory testing for *sickle cell disease* should occur no later than 2 months of age. Because 50% of children with permanent *congenital hearing loss* have no identifiable risk factors, the USPSTF recommends that universal (as opposed to targeted) screening for hearing loss be completed before 1 month of age. Early detection improves language outcomes. Additional audiologic and medical evaluation before 3 months of age for confirmatory testing is warranted for those who do not pass the newborn screening, and infants with risk indicators should undergo periodic monitoring for 3 years. Although the USPSTF has not made a recommendation for *CCHD screening*, the SACHDNC recommended pulse oximetry after 24 h of age but before discharge for early detection of serious heart defects that could require specialized care within the first year of life.

Birth to 2 Years: Infants should have a follow-up visit within 3–5 days of birth and within 48–72 h after hospital discharge to prevent problems related to *feeding, jaundice,* and *weight loss*. Well-infant and child visits for developmental screening and monitoring should occur at ages 1, 2, 4, 6, 9, 12, 15, 18, and 24 months. The CDC recommends using WHO growth standards (http://www.cdc.gov/growthcharts/who_charts.htm). Screening should encompass length, weight, and head circumference. Dental referral is recommended by the first birthday. The USPSTF found insufficient or inconsistent evidence to recommend for or against the routine use of brief, formal screening instruments in primary care to detect *speech and language delay* in children up to 5 years of age. In contrast, the AAP recommends developmental surveillance to identify infants at risk for developmental delays at every well-child preventive care visit through the age of 5 years. Surveillance consists of asking about parents' concerns, obtaining a developmental history, identifying risk and protective factors, and interacting and making observations of the child. Per AAP recommendations, children with Medicaid are mandated to periodically receive a standardized developmental screening test (e.g., Ages & Stages Questionnaires (ASQ), Infant Development Inventory). *Autism-specific screening* for all children at 18 and either 24 or 30 months is also recommended. Additional screening might be needed by children at high risk for developmental problems due to preterm birth or intrauterine growth restriction.

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Table 1 Comparison of USPSTF A and B recommendations with corresponding recommendations from the American Academy of Pediatrics

The USPSTF and the AAFP recommend that clinicians discuss these preventive services with eligible patients and offer them as a priority. All these services have received an "A" or a "B" (recommended) grade from the task force		
Recommendation	**USPSTF[a]**	**American Academy of Pediatrics[b]**
Measurements		
Obesity (body mass index)	Screen children and adolescents aged 6 years and older	24 and 30 months, yearly until 21 years of age
Length/height and weight	No recommendation	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, 18, 24, 30 months; yearly from 3 to 21 years of age
Head circumference	No recommendation	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, 18, and 24 months
Weight for length	No recommendation	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, and 18 months
Hypertension	Insufficient evidence	Annually beginning at 3 years of age. Measurement in infants and children with specific risk conditions should be performed at visits before age 3 years
Physical examination	No recommendation	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, 18, 24, 30 months; yearly from 3 to 21 years of age At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped
Sensory screening		
Vision	Screen children ages 3 to 5 years at least once to detect amblyopia or its risk factors	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, 18, 24, 30 months; yearly from 3 to 21 years of age A visual acuity screen is recommended at ages 4 and 5 years, as well as in cooperative 3-year-olds. Instrument-based screening may be used to assess risk at ages 12 and 24 months, in addition to the well visits at 3 through 5 years of age
Hearing loss	Elected not to update 2008 recommendation and noted that the previous evidence review and recommendation may be outdated	Newborn, 3–5 days to 2 months,4, 6, 9, 12, 18, 24, 30 months; yearly from 3 to 10 years, 11–14, 15–17, and 18–21 years of age
Developmental/behavioral health		
Developmental screening	No recommendation	9, 18, and 30 months
Autism spectrum disorder (ASD)	Insufficient evidence to make a recommendation	18 and 24 months
Developmental surveillance	No recommendation	Newborn, 3–5 days, 1 month; 2, 4, 12, 15, 24, and 30 months, 3 years and yearly until 21 years of age
Psychosocial/ behavioral assessment	No recommendation	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, 18, 24, 30 months; yearly from 3 to 21 years of age Family centered and may include an assessment of child social-emotional health, caregiver depression, and social determinants of health

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Table 1 (continued)

Tobacco use in children and adolescents	*Draft recommendation as distributed for receipt of public comments* Primary care-feasible behavioral interventions, including education or brief counseling, to prevent tobacco use in school-aged children and adolescents have a moderate net benefit. Adequate evidence that behavioral counseling interventions, such as face-to-face or telephone interaction with a healthcare provider, print materials, and computer applications, can have a moderate effect	Yearly, beginning at age 11 years[c] Ask and provide counseling about tobacco use and tobacco smoke exposure as part of health supervision visits and visits for diseases that may be caused or exacerbated by tobacco use. Include tobacco use prevention as part of anticipatory guidance. Address parent/caregiver tobacco dependence as part of pediatric healthcare. Offer treatment and/or referral to adolescents who want to stop smoking. Do not recommend electronic nicotine delivery systems for tobacco dependence treatment. Counseling about strategies to reduce the child's tobacco smoke
Unhealthy alcohol use in adolescents	Insufficient evidence to make a recommendation Note: The AAFP recognizes the avoidance of alcohol products by adolescents aged 12–17 years is desirable. However, the effectiveness of the physician's advice and counseling in this area is uncertain	Annually beginning at 11 years of age. Use the CRAFFT to screen for high-risk alcohol and other drug use disorders simultaneously C – have you ever ridden in a *car* driven by someone (including yourself) who was "high" or had been using alcohol or drugs? R – do you ever use alcohol or drugs to *relax*, feel better about yourself, or fit in? A – do you ever use alcohol/drugs while you are by yourself, *alone*? F – do you ever *forget* things you did while using alcohol or drugs? F – do your family or *friends* ever tell you that you should cut down on your drinking or drug use? T – have you gotten into *trouble* while you were using alcohol or drugs?
Illicit drug use	Update in progress	
Depression screening	Adolescents (age 12–18) when systems are in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up	Adolescent patients ages 12 years and older should be screened annually for depression (MDD or depressive disorders) with a formal self-report screening tool either on paper or electronically (universal screening)
Maternal depression screening	All adults including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up	Routine screening for postpartum depression should be integrated into well-child visits at 1, 2, 4, and 6 months of age

[a]USPSTF A and B recommendations by date. US Preventive Services Task Force. December 2019. https://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/

[b]Note that AAP Bright Futures recommendations are more comprehensive than those of the USPSTF. The above table is an abridgement. Complete AAP recommendations may be found at Bright Futures/AAP Recommendations for preventive pediatric healthcare (Periodicity Schedule). Available at URL: https://www.aap.org/en-us/documents/periodicity_schedule.pdf. Accessed 4 Feb 2020

[c]AAP Section on Tobacco Control. Clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke. Pediatrics 2015. 136(5):1008–1017. https://doi.org/10.1542/peds.2015-3108

The USPSTF found insufficient evidence to recommend universal screening for *iron deficiency anemia (IDA)* in asymptomatic children ages 6–12 months. In contrast, the AAP recommends universal screening for anemia via hemoglobin concentration at approximately 1 year of age.

2 to 10 Years: *Well-child visits* should occur at 24 and 30 months and once every year thereafter. The family physician should ask questions about

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Table 2 Comparison of USPSTF A and B recommendations with corresponding recommendations from the American Academy of Pediatrics for high-risk populations

Procedures	USPSTF	AAP
Newborn blood screening	Referred to discretionary advisory committee on heritable disorders in newborns and children	Screen in the newborn period (confirm initial screen was accomplished, verify results, and follow up, as appropriate. The recommended uniform screening panel (RUSP) **and** screen from 3 to 5 days to 2 months (verify results as soon as possible, and follow up, as appropriate)
Newborn bilirubin	Elected not to update its 2009 recommendation and notes that the previous evidence review and recommendation may be outdated	Confirm initial screening was accomplished, verify results, and follow up, as appropriate. Screen for jaundice and its risk factors before they leave the hospital and conduct a follow-up visit when a baby is 3–5 days old, when bilirubin levels peak. Frequent breastfeeding in the first few days of life also is recommended
Critical congenital heart disease	Part of RUSP (recommended uniform screening panel) (referred)	Newborns using pulse oximetry after 24 h of age, before discharge
Developmental dysplasia of the hip (DDH)	Insufficient evidence to make a recommendation	Hip imaging for female infants born in the breech position and optional hip imaging for boys born in the breech position or girls with a positive family history of DDH
Immunizations	Referred to advisory committee on immunization practices (ACIP) (http://www.cdc.gov/vaccines/schedules/index.html)	Schedules, per the AAP Committee on Infectious Diseases, are available at http://redbook.solutions.aap.org/. Every visit should be an opportunity to update and complete child's immunizations
Anemia	Insufficient evidence to make a recommendation	Assess at 4, 12, 15, 18, 24, and 30 months and yearly beginning at 3 years of age
Lead poisoning	Insufficient evidence to make a recommendation in children 1–5 years of age	Assess at 6, 9, 12, 24 months and at 3, 4, 5, and 6 years. "It is now clear that there is no known threshold below which adverse effects of lead are absent." **12 and 24 month alternative:** Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high-prevalence areas at 12 and 24 months
Tuberculosis	No A or B recommendation for infants or children	Assess at 1, 6, 12, 24 months and yearly from 3 to 21 years
Dyslipidemia	Insufficient evidence to make a recommendation (up to age 20 years)	Asses risk at 2, 4, 6, and 8 years of age. Universal lipid screen between 9 and 11 years of age
Sexually transmitted diseases	Screen for chlamydia and gonorrhea in sexually active women age 24 years and younger	Annually beginning at 11 years of age. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the AAP Red Book: Report of the Committee on Infectious Diseases

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Table 2 (continued)

HIV infection, screening	All adolescents and adults ages 15–65 years and others who are at increased risk for HIV infection and all pregnant women Note: The AAFP's endorses the CDC recommendation to initiate routine screening at age 13 years	Once between the ages of 15 and 18, make every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually
Oral health		
Fluoride varnish: dental caries prevention	Apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption	Oral health assessment for all children by age 6 months and a first dental visit by age 1 year
Fluoride supplementation	Oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride (<0.6 ppm F)	Oral fluoride supplementation and application of fluoride varnish in children at risk for dental caries
Anticipatory guidance		
Anticipatory guidance	No recommendation	Newborn, 3–5 days, by 1 month; 2, 4, 6, 9, 12, 18, 24, 30 months; yearly from 3 to 21 years of age
Skin cancer counseling	Aged 10–24 years who have fair skin High risk: fair skin, freckles, atypical nevi, >50 moles, increased lifetime or intense sun exposure	Sun safety advice during health maintenance visits at least once per year
Suicide risk in adolescents, adults, and older adults	Insufficient evidence to make a recommendation	Recommends to ask questions about mood disorders, sexual orientation, suicidal thoughts, and other risk factors associated with suicide during routine healthcare visits
Child maltreatment	Insufficient evidence to make a recommendation	Use the parent screening tool to screen for risk factors: a Safe Environment for Every Kid (SEEK). http://brightfutures.aap.org/pdfs/Other%203/PSQ_screen.pdf
Counseling about proper use of seatbelts and avoidance of alcohol use to prevent injury	Refers clinicians to the CDC's Community Guide recommendations: laws mandating use, distribution and education programs, community-wide information and enhanced enforcement campaigns. (http://www.thecommunityguide.org)	Counseling and demonstrating the use of child safety seats. Insufficient evidence about counseling for other restraints and to discourage driving under the influence of the alcohol

injury/illness, visits to other healthcare providers, and changes in the family or home and should also address any parental concerns. During these well-child visits, the child's growth and development should be measured, and testing for vision and hearing starting at age 3 years should be performed. A dental home should be established in addition to a medical home, and a preventive visit to the dentist should occur twice per year. During this period, parents often have questions about their child's behavior and social functioning. *Developmental milestones* and observation of parent and child interaction should also be included at every preventive care visit. If needed, intervention by age 3 years can greatly improve a child's development and learning ability. Developmental surveillance in school-aged children can be monitored by asking about school performance to identify the need to test for learning disabilities.

The CDC has recommended growth charts for *monitoring growth* from ages 2 years and older

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(http://www.cdc.gov/growthcharts/clinical_charts.htm), and *body mass index (BMI)* should be calculated at least annually. Overweight and obesity are defined as an age-gender-specific BMI's between the 85th and 95th percentiles and ≥95th percentile, respectively. Screening for obesity in children aged 6 years and older and referral for intensive counseling are recommended by the USPSTF, including interventions for diet and physical activity (Table 1). Interventions that focus on younger children should also incorporate parental involvement as a component.

The USPSTF found insufficient evidence to support screening for *primary hypertension* in asymptomatic children and adolescents (before 18 years of age). Furthermore, although there is good evidence that *dyslipidemia* during childhood increases risks in adulthood, the clinical health benefits shown in adults identified and treated for dyslipidemia have not been studied in children, making the role of screening children uncertain (USPSTF Grade I). In contrast, the National Heart, Lung, and Blood Institute (NHLBI) recommends that children ages 3 years and older have blood pressure measurement at least once at every "healthcare episode." The NHLBI also recommends universal lipid screening between 9 and 11 years of age and selective screening in children and adolescents with a family history of premature coronary heart disease (CHD), a parent with dyslipidemia, or high-risk condition such as diabetes, obesity, or hypertension [26].

11 to 18 Years: Preventable conditions remain the leading causes of morbidity and mortality among adolescents. *Health risk behaviors* (e.g., alcohol and drug use, unsafe sexual practices, etc.) are major contributors to unintentional injuries such as motor vehicle collisions, intentional injuries such as homicide and suicide, and sexual risk behaviors leading to sexually transmitted infections (STIs) and unintended pregnancy. The AAP recommends screening adolescents for high-risk alcohol and other drug use disorders simultaneously beginning at 11 years of age and annually thereafter using the CRAFFT six-item tool (Car, Relax, Alone, Forget, Friends, Trouble) (Table 1).

Obesity has become a major cause of adolescent morbidity. It is a contributor to a dramatic increase in the number of youth with type 2 diabetes mellitus, and it is the strongest risk factor for primary hypertension in children and adolescents. BMI measurement should be standard during health maintenance visits, and patients with excess weight should be referred for counseling and comprehensive weight management programs that include dietary, physical activity, and behavioral counseling.

Sexually active teens should be screened for *STIs* including *chlamydia* and *gonorrhea*. Young women (ages 15–24) account for 44% of reported cases of chlamydial infection and face the most severe consequences of an undiagnosed infection. Because adolescents are a vulnerable population at increased risk of *HIV infection*, assessment for high-risk behaviors and screening for HIV should be standard. The USPSTF advises one-time screening beginning at age 15 years to identify persons who are already HIV-positive, with repeated screening of those who are known to be at risk for HIV infection, those who are actively engaged in risky behaviors, and those who live or receive medical care in a high-prevalence setting (Table 2). Although such testing is generally performed without a separate written informed consent or pretest counseling, providers must anticipate that some patients are poorly equipped to deal with a positive HIV test result and assure that appropriate support is available.

Major depressive disorder (MDD) among adolescents, often undiagnosed and untreated, is a disabling condition that is associated with increased risk of suicide, decreased school performance, poor social functioning, early pregnancy, increased physical illness, and substance abuse. Important risk factors that can be assessed relatively accurately and reliably include parental depression, the presence of comorbid mental health or chronic medical conditions, and a major negative life event in the patient's life. The Patient Health Questionnaire for Adolescents [PHQ-A] and the Beck Depression Inventory for Primary Care Version [BDI-PC] have been used successfully in adolescents to screen for MDD [27].

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Prevention at Ages over 18 Years

Immunization

A recommendation by a patient's healthcare provider for needed vaccines is a strong predictor of patients receiving recommended vaccines. The ACIP annually reviews and updates the "Recommended Immunization Schedule for Adults Ages 19 Years or Older" (Fig. 3). With the exception of the yearly *influenza* vaccination, which is recommended for all adults, recommendations for adults target different populations based on age, health conditions, behavioral risk factors (e.g., injection drug use), occupation, travel, and other indications.

The ACIP recommends beginning *zoster* vaccination at age 50 years with recombinant zoster vaccine (preferred) or 60 years and older with zoster vaccine live. For *pneumococcus bacteria*, all adults 65 years of age or older receive a dose of PCV13 followed 6–12 months later by a dose of PPSV23. If a dose of PPSV23 cannot be given during this time window, it should be administered during the next doctor's visit. PCV13 protects against 13 strains of pneumococcus bacteria, and PPSV23 protects against 23 strains of pneumococcus bacteria. Both vaccines provide protection against meningitis and bacteremia. PCV13 also provides protection against pneumonia. *Hepatitis B vaccine* is recommended for all unvaccinated adults at high risk for HBV infection and diabetic adults <60 years. For patients with diabetes ≥ 60 years, vaccination may be warranted based on likelihood of acquiring hepatitis B and immune response. A single dose of *Tdap* is recommended for all adults aged 19 years and older who have not received Tdap previously regardless of the interval since the last dose of Td. Adults should also receive a Td booster every 10 years. Tdap should be administered to pregnant women during each pregnancy (preferred during 27–36 weeks gestation) regardless of interval since prior Td or Tdap vaccination. Pregnant women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the healthcare facility. Vaccination for *varicella*, *zoster*, and *MMR* is contraindicated in pregnancy and immune-compromising conditions (safe in patients with HIV who have CD4 ≥ 200 cells/μL).

Prophylaxis

Folic acid prophylaxis (400 micrograms per day) is recommended through age 45 years to prevent neural tube defects. The USPSTF considers *low-dose aspirin* (81 mg/day) to be of substantial benefit for pregnant women at high risk for preeclampsia (grade B recommendation). Risk factors for preeclampsia include autoimmune disease, hypertension, multiple gestation pregnancy, renal disease, diabetes, and history of preeclampsia (Table 4). Low-dose aspirin therapy can also be considered for those with multiple moderate risk factors. Recommendations for increasing bone strength include *calcium* and *vitamin D supplementation*. The USPSTF also recommends that clinicians engage in shared, informed decision-making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer risk-reducing medications, such as *tamoxifen or raloxifene*.

Counseling and Anticipatory Guidance

Preventive counseling and services are an important component of the health maintenance visit. The family physician should emphasize a shared decision-making approach including unique goals of prevention, life expectancy, comorbidities, potential for harms, and patient values and preferences. Preventive services are more likely to be discussed when patients have an established relationship with an identified clinician. The five leading causes of death – comprising almost two-thirds of all US deaths – are *heart disease*, *cancer*, *stroke*, *lung disease* (*emphysema*, *chronic bronchitis*), and *unintentional injuries* (especially motor vehicle collisions, medication overdoses).

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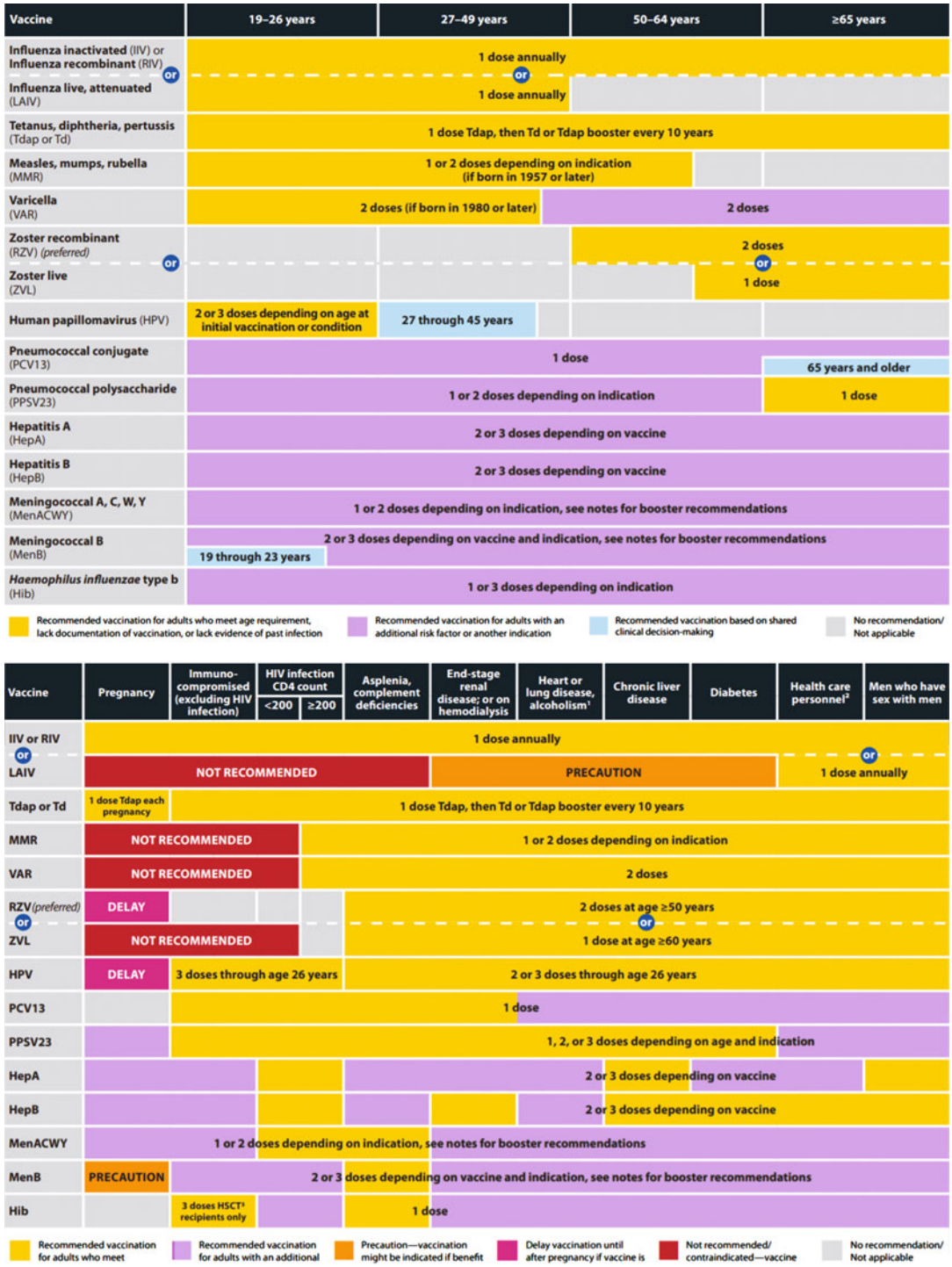


Fig. 3 Recommended adult immunization schedule – United States, 2020. Note: The above recommendations must be read along with the footnotes of this schedule. See https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. The recommendations in this schedule are in effect as of January 1, 2020, by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices. Additional

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Counseling comprises recommendations for healthy lifestyle and intensive behavioral counseling for adults with known risk factors for *coronary heart disease* and *diet-related chronic disease*. The family physician should also advise on the importance of regular physical activity including aerobic, strength, and flexibility training in the prevention of disease and non-traumatic weight-bearing exercise (e.g., walking) for osteoporosis prevention. All patients should be asked about *tobacco* use and provided tobacco cessation interventions. Brief counseling within primary care for smoking cessation increases quit rates and decreases cardiovascular risk. Clinicians have many resources to help patients stop smoking. The CDC has developed a website with many such resources, including information on tobacco quit lines, available in several languages (www.cdc.gov/tobacco/campaign/tips). It is also recommended to assess any history of *alcohol/drug* use. Brief questionnaires (e.g., Alcohol Use Disorders Identification Test (AUDIT)) may help clinicians assess the likelihood of problems or hazardous drinking. Patients should receive behavioral counseling about the effects of alcohol and substance use, including prescription and over-the-counter drugs. Brief interventions in primary care, including feedback, goal setting, and follow-up with short contacts, are effective in reducing alcohol consumption. High-intensity behavioral counseling to prevent *STIs* for adults who are at increased risk of STIs is also recommended. Older adults continue to be sexually active in their later years. In fact, the rate of STIs has more than doubled among middle-aged adults and the elderly over the last decade. The lack of awareness about STIs and their prevention may be contributing to the increasing reported rates. It is important to provide counseling and offer STI testing to those at risk.

Because women may not be aware of *pregnancy* in its earliest stages, patients should be counseled in advance about the adverse effects of obesity, alcohol, illicit drugs, tobacco, and other environmental exposures. If a patient has a BMI $\geq$30, weight loss is recommended before becoming pregnant. Women should be advised that there is no known safe level of alcohol consumption during pregnancy and the harmful effects of alcohol and recreational drug use on fetal development should be stressed. Counseling should emphasize that smoking during pregnancy can cause infant death and is associated with increased risk for premature birth and intrauterine growth retardation. Smoking cessation counseling sessions should be provided, augmented with messages and self-help materials tailored for pregnant smokers as needed.

Screening

The USPSTF recommends screening for four cancer sites – *cervix*, *female breast*, *colorectal*, and *lung.* It does not favor *prostate* cancer screening. Most patients with *cervical cancer* are women younger than 50 years, and most invasive cervical cancers occur in women lacking appropriate screening during the 5 years immediately preceding diagnosis. Cervical cancer screening is not recommended before age 21 regardless of when sexual activity begins. Screening should usually be stopped at age 65 if adequate screening was carried out in the preceding 10 years. Also, if the patient had a total hysterectomy (with complete cervical removal) for benign disease, screening is not necessary. For *breast cancer*, family history and age are key risk factors. The USPSTF recommends biennial mammography for women ages 50–74 years, while the American Cancer Society recommends that annual mammography begins at age 40 and continues so long as the woman is in good health. Women with a family history sug-

Fig. 3 (continued) information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at www.cdc.gov/vaccines. Report any suspected cases of reportable vaccine-preventable diseases or outbreaks to the local or state health department. Report clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System at www.vaers.hhs.gov or 800–822-7967.

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gestive of breast and ovarian cancer syndrome should receive counseling for options which may include genetic testing for BRCA1 and BRCA2 and more intensive screening for breast cancer. The harms resulting from screening for breast cancer include psychological distress, unnecessary imaging tests and biopsies in women without cancer, and inconvenience due to false-positive screening results. Partly because such problems may be accentuated by annual mammography, the USPSTF recommends against annual testing even though models used by the Task Force suggest that annual testing brings a survival advantage. The ACA requires insurers to cover screening mammograms every 1–2 years for women ages 40+ years.

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths and the third most common cancer among American men and women. Early detection and removal of precancerous polyps before CRC develops reduce mortality. Screening is recommended for all adults aged 50–75 years. Although the percentage of US adults aged 50–75 years who were up to date with colorectal cancer screening increased 1.4% points, from 67.4% in 2016 to 68.8% in 2018, screening rates remain far below what would be necessary to decrease incidence and mortality. Strategies to increase screening rates besides clinician recommendation include patient and clinician reminders, decision aids, and organization of office staff to support a program of patient education, monitoring, outreach, and follow-up (e.g., patient navigator, FOBT cards). *Lung cancer* is the leading cause of cancer-related death and the second most common in the US. Prevention of tobacco use, which accounts for nearly 85% of all US lung cancer cases, is the most important intervention to prevent the disease. Although lung cancer screening is not an alternative to smoking cessation, screening high-risk patients aged 55–80 years with low-dose computer tomography (LDCT) is recommended by the USPSTF. Current smokers should be informed of their continuing risk for lung cancer and offered cessation treatments. Screening with LDCT should be viewed only as an adjunct to tobacco cessation interventions. The Task Force does not recommend screening for *prostate cancer* for men in the general US population. Most cases of prostate cancer have a good prognosis, even without treatment, and the lifetime risk of dying from the disease is 2.8%. In addition, the mortality benefits of PSA-based prostate cancer screening are, at best, small and potentially none, while the harms are moderate to substantial potentially due to those associated with overdiagnosis and overtreatment (need for biopsy and impotence or incontinence occurring in at least 50% of men who undergo treatment for a disease that may be indolent).

Overweight, obesity, and *lack of physical activity* are associated with hypertension, diabetes, increased cardiovascular events, and increased all-cause mortality. The USPSTF recommends that clinicians screen their adult patients for obesity and offer or refer them if appropriate to intensive, multicomponent behavioral programs promoting healthy eating, increasing physical activity, or both. In nutrient-sufficient adults, evidence is insufficient to support multivitamin supplementation to prevent cancer and cardiovascular disease. In 2017, the American College of Cardiology and the American Heart Association published new guidelines for hypertension management and defined hypertension as a blood pressure at or above 130/80 mmHg. *Hypertension* affects approximately 45% of adult Americans, and it is a major risk factor for ischemic heart disease, left ventricular hypertrophy, renal failure, stroke, and dementia. Screening for hypertension in adults 18 and over is recommended by the USPSTF. In addition, the Task Force recommends screening for *abnormal blood glucose* as part of cardiovascular risk assessment in adults aged 40–70 years who are overweight or obese. The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (i.e., symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) ages 40–75 years; (2) one or more CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking); and (3) a calculated 10-year risk of a

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cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk require universal lipid screening in adults aged 40–75 years.

Combined *syphilis*, *chlamydia*, and *gonorrhea* continue to be serious public health problems in the United States. The USPSTF recommends screening in sexually active women age 24 and younger and in older women at increased risk for infection (history of chlamydial or other STIs, new or multiple sexual partners, inconsistent condom use, and exchanging sex for money or drugs). Recommendations for *HIV* differ regarding age for screening. The USPSTF recommends one-time screening through age 65 years, while the suggested CDC cutoff is 64 years. The American College of Physicians suggests expanding the age range to 75 years due to the growing number of older adults with HIV infection. Screening for *hepatitis B*, *hepatitis C*, and *syphilis* should be offered to all persons at high risk for infection (Table 3). The USPSTF recommends screening all adults for *depression* when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up. "Staff-assisted depression care supports" refer to clinical staff (e.g., nurse specialists) who assist the primary care clinician by providing some direct depression care including coordination, case management, or mental health treatment. Several screening tools are available; however, asking two simple questions about mood and anhedonia (Table 4) may be as effective as using more formal instruments. *Intimate partner violence* (*IPV*) and *abuse of elderly and vulnerable adults* often remain undetected. Nearly 25% of women and 14% of men have experienced the most severe types of IPV in their lifetime. Victims of IPV, which refers to physical, sexual, or psychological harm by a current or former partner or spouse, often develop chronic mental health conditions, such as depression, posttraumatic stress disorder, anxiety disorders, substance abuse, and suicidal behavior. Risk factors for IPV include young age, substance abuse, marital difficulties, and economic hardships. Available screening instruments can identify current and past abuse or increased risk for IPV, but for vulnerable adults, the USPSTF found inadequate evidence on the accuracy of screening instruments. Most *abdominal aortic aneurysms (AAA)* ($\geq$3 cm) are asymptomatic until they rupture, and they are also most prevalent in men who have ever smoked. Although the risk for rupture varies greatly by aneurysm size, the associated risk for death is as high as 75–90%. Therefore, considering an effective method for screening and treating appropriate patients before rupture is important. One-time ultrasound screening for AAA in men ages 65–75 years who are current or former smokers is recommended. Selective screening in this age group who have never smoked should be considered if risk factors for AAA are present (e.g., first-degree relative with an AAA, history of other vascular aneurysms, cardiovascular disease, cerebrovascular disease, atherosclerosis, hypercholesterolemia, obesity, or hypertension).

Effectively reducing *bone fractures* among older people involves both preventing falls and increasing bone and muscle strength. Older adults should be asked about recent falls. Fall prevention includes minimizing psychotropic medications and encouraging weight-bearing physical activity and muscle strengthening. The USPSTF recommends routine osteoporosis screening in women aged 65 and older and for those at increased risk most commonly with dual-energy X-ray absorptiometry (DXA) and quantitative ultrasonography. Routine screening for *osteoporosis* is not recommended for young postmenopausal women who do not meet risk factor-based criteria. *Depression in older adults* is often misdiagnosed and undertreated having a significant adverse impact on quality of life, health outcomes, healthcare utilization, morbidity, and mortality. Medicare beneficiaries with chronic diseases and associated depression have significantly higher healthcare costs than those with chronic diseases alone. Also, suicide rates are almost twice as high in the older adult compared with

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Table 3 USPSTF A and B recommendations for adults

Grade	Recommendations	Description[a]
Screening		
B	Unhealthy alcohol use: screening and behavioral counseling interventions	Screen adults 18 years or older, including pregnant women, and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use. **NIAAA Single Alcohol Screening Question (SASQ)**: *"How many times in the past year have you had 5 [for men] or 4 [for women and all adults older than 65 years] or more drinks in a day?"* **AUDIT-C alcohol screening:** 1. How often did you have a drink containing alcohol in the past year? 2. How many drinks did you have on a typical day when you were drinking in the past year? 3. How often did you have 6 or more drinks on one occasion in the past year?
B	Depression screening	In the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up
A	Blood pressure (BP) Hypertension	Screening for high blood pressure in adults aged 18 and over. The USPSTF recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment
A	HIV infection: screening	Persons aged 15–65 years, all pregnant women, and persons who are at increased risk (MSM, IDU, having sex partners who are HIV-infected, unprotected vaginal/anal intercourse, bisexual, exchanging sex for drugs or money
B	Hepatitis B virus infection: screening	Persons at high risk for infection including all foreign born in countries with a high rate of infection, regardless of vaccination history, mainly Asia, sub-Saharan Africa, the Pacific Islands, the Middle East, and Eastern Europe. Also injection drug users; MSM; household contacts and sexual partners of HBsAg-positive persons; patients receiving hemodialysis; and immunosuppressed and HIV-positive persons
A	Syphilis infection: screening	Persons at increased risk for syphilis infection including MSM and engage in high-risk sexual behavior, commercial sex workers, persons who exchange sex for drugs, and those in adult correctional facilities
A	Latent tuberculosis infection (LTBI): screening	Populations at increased risk for LTBI based on increased prevalence of active disease and increased risk of exposure include persons who were born in/former residents of countries with increased tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings (e.g., homeless shelters and correctional facilities)
B	Breast and ovarian cancer/ BRCA risk assessment and genetic counseling/testing	Primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing

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Table 3 (continued)

Grade	Recommendations	Description[a]
B	Intimate partner violence screening	In women of reproductive age and provide or refer women who screen positive to ongoing support services
B	Chlamydia and gonorrhea: screening	Sexually active women age ≤24 years and in older women who are at increased risk for infection (prior STIs, HIV, new or multiple sex partners, exchanging sex for money or drugs). Insufficient evidence for screening in men
A	Cervical cancer	Women age 21–29 years with cytology alone every 3 years. For women age 30–65 years every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting)
B	Hepatitis C: screening	Persons at high risk for infection (past or current injection drug use; blood transfusion before 1992) and 1-time screening for adults born between 1945 and 1965
B	Abnormal blood glucose/ and type 2 diabetes mellitus	As part of cardiovascular risk assessment in adults aged 40–70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity
A	Colorectal cancer (CRC)	Screening in adults ages 50–75 years. The risks and benefits of different screening methods vary
B	Breast cancer screening, mammography	Biennial screening for women 50–74 years. Women 40–49 years should be individualized and take into account patient's risks and values regarding specific benefits (Grade C)
B	Osteoporosis to prevent fractures	Screening with bone measurement testing to prevent osteoporotic fractures in women ≥65 years and in postmenopausal women ≤65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool
B	Lung cancer: screening	Annually with LDCT in adults aged 55–80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years
B	Abdominal aortic aneurysm (AAA), men	One-time screening by ultrasonography in men ages 65–75 years who have ever smoked (≥100 cigarettes). Selectively offer screening for AAA in men ages 65–75 years who have never smoked (C)
Preventive therapies		
A	HIV preexposure prophylaxis	Preexposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition
B	Breast cancer, prevention medication	Clinicians offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene, for women who are at increased risk for breast cancer and at low risk for adverse medication effects[b]
A	Folic acid for prevention of neural tube defects	All women planning or capable of pregnancy take a daily supplement containing 0.4–0.8 mg (400–800 μg) of folic acid
C	Aspirin use to prevent cardiovascular disease and colorectal cancer	Low-dose aspirin in adults aged 40–59 years who have a 10% or greater 10-year CVD risk and are not at increased risk for bleeding.

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Table 3 (continued)

Grade	Recommendations	Description[a]
B	Statin use for the primary prevention of CVD	Adults aged 40–75 years with no history of CVD, 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater
B	Falls prevention in community-dwelling older adults	Exercise interventions to prevent falls in community-dwelling adults 65 years or older who are at increased risk for falls
Counseling		
A	Tobacco smoking cessation	Ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and US Food and Drug Administration (FDA)-approved pharmacotherapy for cessation to adults who use tobacco
B	Sexually transmitted infections	Intensive behavioral counseling for all sexually active adolescents and for adults who are at increased risk for STIs
B	Weight loss to prevent obesity-related morbidity and mortality in adults	Clinicians should offer or refer adults with a BMI of $\geq$30 kg/m^2 to intensive, multicomponent behavioral interventions
B	Healthful diet and physical activity for CVD prevention in adults with cardiovascular risk factors	Offering or referring adults who are overweight or obese and have additional cardiovascular disease (CVD) risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention
B	Skin cancer prevention	Counseling young adults, adolescents, children, and parents of young children about minimizing exposure to ultraviolet (UV) radiation for persons aged 6 months to 24 years with fair skin types to reduce their risk of skin cancer

[a]USPSTF A and B Recommendations. US Preventive Services Task Force. December 2019. AHRQ, with permission. http://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/

[b]Breast Cancer Risk Assessment Tool (available at www.cancer.gov/bcrisktool) is based on the Gail model and estimates the 5-year incidence of invasive breast cancer in women on the basis of characteristics entered into a risk calculator. This tool helps identify women who may be at increased risk for the disease

[c]In most cases the AAFP agrees with the USPSTF. Circumstances where there are differences have been noted. Summary of Recommendations for Clinical Preventive Services. July 2017. AAFP, with permission. http://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/cps-recommendations.pdf

[d]JNC7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. http://www.nhlbi.nih.gov/files/docs/guidelines/express.pdf

the general population, with the rate highest for white men over 85 years of age.

Adhering to Prevention Guidance: Barriers to Care

Barriers to conducting preventive care services may be due to the medical care providers or patients. This section summarizes those barriers and addresses a few techniques to implement in practice to improve patient and provider compliance with preventive care.

Barriers to Provider Adherence

Provider adherence is related, in part, to the challenges of a busy practice, system barriers, or simple human error. Common reasons for provider gaps in preventive care could be due to lack of awareness of guidelines, lack of familiarity with guidelines, lack of agreement, lack of outcome expectancy, and external barriers such as patient and environmental factors [28]. The following sections consider these barriers in more detail.

Time Constraint: Time constraints affect even the most prevention-oriented providers. Patients

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Table 4 USPSTF A and B Recommendations for pregnant women

Recommendations for pregnant women		
B	Preeclampsia: screening	Blood pressure measurements throughout pregnancy
B	Preeclampsia: low-dose aspirin	Low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia
B	Asymptomatic bacteriuria	Urine culture for pregnant women at 12–16 weeks gestation or at their first prenatal visit
A	Hepatitis B virus infection	Pregnant women at their first prenatal visit
A	Human immunodeficiency virus (HIV) infection	All pregnant persons, including those who present in labor or at delivery whose HIV status is unknown
A	Syphilis infection	Early screening for syphilis infection in all pregnant women
A	Rh (D) incompatibility: screening	Rh (D) blood typing and antibody testing at the first visit for pregnancy-related care. Repeated Rh (D) antibody testing for all unsensitized Rh (D)-negative women at 24–28 weeks gestation, unless the biological father is known to be Rh (D)-negative (B)
B	Breastfeeding: counseling	Interventions during pregnancy and after birth to promote and support breastfeeding

presenting for annual well-exams offer the best opportunity to perform indicated preventive services, as patients are then most receptive to prevention, provider time constraints are addressed, and payment is likely to be covered. In compliance with the Affordable Care Act, insurances commonly waive the co-pay and deductible for preventive visits. When patients present with complaints that use up the allotted visit time to assess, diagnose, and treat, it is likely to limit the capacity of the family physician to provide preventive care. The Annual Wellness Visit (AWV) required by the Centers for Medicare & Medicaid Services (CMS) could be utilized as an opportunity to perform preventive services. Furthermore, some services may require time-consuming patient education or counseling. Often practices must reevaluate the delegation of duties and team-based care, shifting some responsibilities to nursing and other staff in order to allow providers to cover the preventive service needs of most patients. For example, estimations show that full adherence to USPSTF recommendations could require 7.3 physician hours out of each working day [29].

Training Needs: Training is a key component of overall practice compliance with the provision of preventive services. It is essential to ensure that the staff is skilled at providing the services required, such as standing orders for vaccination and screenings. In addition, they should be knowledgeable about brief intervention for alcohol and drug use, depression, and lifestyle changes. Barriers include the knowledge base and practice patterns of providers (awareness, familiarity, and agreement with guidelines). Awareness and familiarity with guidelines could be partially addressed through continuing medical education. Other factors may require more extensive training and possibly systematic practice change. Confusion may also stem from updates to guidelines and/or conflicting recommendations from different organizations.

Coding and Billing Difficulties: Though electronic medical record (EMR) systems with billing systems are quickly becoming standard tools with important potential benefits, they are not uniform in their interfaces, features, or data entry requirements. In some instances, EMR may introduce new challenges into daily practice. Receiving reimbursement for preventive services may be difficult. However, it is encouraging that the list of covered preventive services grows more comprehensive annually, particularly in light of the Affordable Care Act (ACA). A similar barrier stems from the disparate coverage provided by states in response to federal mandates. For example, Medicaid coverage of preventive services varies between states, and even as the ACA has included the coverage of key preventive services, many states have not expanded their Medicaid programs.

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Practice Culture: Some providers or practices may be resistant to focusing on preventive services. This resistance can be due to personal prejudices held toward patients (e.g., patients with poor self-care habits or combative attitudes). More importantly, the entire practice may be averse to systematic approaches to implementing preventive services for many reasons, including an orientation toward providing only acute care. In this scenario, the practice-wide goal may be to see as many patients as possible, addressing presenting complaints, with less emphasis on delivering preventive services. This type of practice alignment may even discourage individual attempts to follow prevention guidelines.

Barriers to Patient Adherence

Much like provider compliance, patients may face various barriers that undermine prevention. *Access and Socioeconomic Barriers:* The greatest barrier to patient adherence is a lack of access to preventive services. While cost barriers to regular primary care visits are important, sociodemographically vulnerable groups are also more likely to face other barriers that include transportation, competing time demands, fear, perceptions of risk, and fragmented care [30].

*Health Literacy***:** Health literacy is an important factor impacting patient adherence to preventive care across cultural and socioeconomic groups, and low health literacy, low incomes, and low education are often correlated and low perception of the seriousness of the illness may lead to less preventive health screening [31]. Lifestyle and behavioral health are key components in many of the leading causes of mortality and morbidity in the United States. The prevalence of obesity and type 2 diabetes is example of preventable conditions whose occurrence may indicate a lack of patient knowledge or control over basic lifestyle behaviors. Even when patients are generally knowledgeable about healthy living, they may lack specific knowledge about vaccination, cancer screening, and other preventive services.

Cultural and Demographic Factors: Reviews of preventive service utilization have identified cultural and racial differences when receiving preventive care. However, those differences may be affected by physicians' advice and/or receiving education sessions on preventive screening [32]. Cultural factors may be related to language barriers that affect the rate of receiving preventive care, including cervical cancer screening [33]. Insurance coverage and cost are other essential factors. In some cases, fear, myths, or anecdotes may inhibit a patient from participating in preventive care. Some patients may resist preventive services because they expect a procedure to be uncomfortable. Some may even wish to remain ignorant of any potentially negative test result. Age, lifestyle, obesity, location, previous preventive service, or other medical experiences may all contribute to the likelihood of patient compliance as well [34]. More research is needed to understand the best ways to address these complex factors.

Strategies to Improve Adherence to Prevention Guidance

Addressing *all* patient barriers to preventive care is beyond the scope of this discussion. However, public education, insurance coverage, and a variety of public health campaigns are key features of improving rates of screening and intervention. Preventive services have proven to be cost-effective, cost-saving, and lifesaving in the longer term [35]. Unfortunately, in many cases, the implementation of such services faces practice and provider barriers on the front end. Implementing some of the strategies below may help.

***Training and Time*:** When providers report that they lack training about a new guideline or screening tool, training that targets a particular recommendation may be helpful. This approach requires functional communication between providers and administrators and the will of all parties to solve the problem. Administrators and providers may also proactively collaborate to assess the uptake of new or existing evidence-based guidelines in practice and design improvement programs to facilitate providing the needed

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education and infrastructure to meet goals. However, time constraints can also be addressed in several other ways. Standing orders utilizing nursing staff can effectively shift routine recurring tasks to nursing personnel, such as immunizations and behavioral screenings [36]. Nursing staff effort can be utilized to deliver not only primary preventive services but also secondary and tertiary prevention counseling, case management, care coordination, and even practice management. When well executed, this workflow can improve quality and efficiency [37].

Practice Improvement and Facilitation: Most practices are highly dynamic workplaces, and many experience varying caseloads over time. Even a medium-sized practice may require addressing each of the aforementioned barriers in order to be successful. Practice facilitation, which may include employing or tasking an identified person with the role of helping to get evidence-based guidelines into practice, has been shown effective, and a range of methods are available to initiate this facilitation [38]. Value-based care is making its way into many health markets. Practice facilitation to accommodate value-based care is essential and includes developing registries to track preventive care adherence as well as chronic disease management through care coordination and outreach. Adherence to guidelines and pursuit of high standards of care while maintaining the capacity to meet individual patient needs will be the standard of care in the future [39].

Patient-Centered Medical Home: Perhaps the most widely recognized and comprehensive model for primary care practice improvement is the Patient-Centered Medical Home (PCMH) model. Adopted and developed by the American Academy of Pediatrics, American Academy of Family Physicians, the American College of Physicians, and the American Osteopathic Association, the PCMH principles include a personal physician for each patient; whole-person care, including preventive services; integrated and coordinated care including mental and behavioral health; quality and safety standards including compliance with evidence-based guidelines; and improved patient access [40]. Ideally, transforming a practice into a PCMH involves addressing many of the provider barriers presented herein, while also aiming to support patient compliance. Making the transition to a PCMH can require significant inputs of human and material resources, depending on the starting point of the particular practice. These inputs include staffing changes and hiring, quality improvement assessment processes, regular planning and evaluation meetings, case management and care coordination system development or improvement, practice culture change, health information technology utilization including electronic medical records, integration of mental and behavioral health, and outreach and dialogue with patients to enhance awareness and feedback.

Special Considerations in Underserved Populations

Practices addressing underserved populations, whether in low-income urban or rural areas, tend to see a higher incidence of preventable disease, less access to treatment, lower health literacy, and, in some cases, mistrust of the healthcare system. These patient-level determinants of health demand higher inputs of resources and time to address long-standing patient needs ranging from counseling to numerous tests or procedures in a given visit. Higher needs combined with lower resources result in larger demands on practices. However, at the same time, this offers an opportunity for the practice to achieve a more significant impact and to identify potential areas for further improvement.

Special Considerations in Teaching Practices

Teaching practices require special training and cultural considerations. Resident physicians are often well equipped with knowledge of the most recent prevention guidelines but may lack the experience to effectively recognize opportunities or counsel patients. Moreover, residency practices have higher turnover of physicians due to the nature of training duration, impacting the practices' ability to create effective long-term

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patient-provider relationships. Continuity clinics, in which family medicine physicians track the same patient group through the entire training period, as well as specific training in behavior change modalities and integrative medicine, may help to address these issues.

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Health Promotion and Wellness

7

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Lifestyle medicine has become a hot topic within the health care field as of late with courses dedicated to learning lifestyle medicine and more physicians learning how to prescribe lifestyle changes. Lifestyle changes such as diet, smoking cessation, and physical activity are all related to patient's overall health and well-being. This chapter will focus on how to help guide your patients to change their lifestyle and reduce preventable diseases.

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Physical Activity

Briefly, exercise can be defined as movement or exercise that requires the body to use energy [1]. Physical activity can be further broken down into subtypes including aerobic activity, muscle-strengthening activity, bone strengthening activity, balance and flexibility activities. Many activities, especially things like walking, running, and weight lifting, for example, cross over several of these subtypes. Striving to include a variety of physical activities may help to optimize fitness.

Benefits of Physical Activity

Physical activity has many immediate and long-term benefits. Some of the notable benefits include improvement in sleep quality, weight loss, neurocognitive benefits, and a sense of general well-being [1]. Longer term benefits include decreases in chronic conditions such as ischemic heart disease, type 2 diabetes mellitus, obesity, and certain cancers, including breast, colon, endometrial, esophageal adenocarcinoma, renal, lung, and certain gastric malignancies [2]. Numerous evidence-based studies demonstrate linkages between physical activity and slowing or stopping disease progression, or even aiding in the reversal of several chronic diseases. For instance, in a randomized trial that compared percutaneous coronary angioplasty with exercise training in 101 patients with stable coronary artery disease, exercise training proved to be superior to percutaneous intervention when comparing both event-free survival and exercise tolerance without symptoms [4]. In patients 65 and older, physical activity has a multitude of benefits, including a decreased rate of falls.

Physical Activity Recommendations

Regarding physical activity, it can be unclear as to what specifically should be recommended to patients. So what counts as exercise and how much exercise is needed to be beneficial? In 2008, the Department of Health and Human Services first issued *Physical Activity Guidelines for Americans* and has since released an updated version 2 of the resource in 2018. The updated resource explains what types and amounts of physical activity yield beneficial results, and highlights ways that health professionals might promote these guidelines.

Current physical activity recommendations include:

- For adults 18 years and older, recommendations include striving for:
  At least 150 min per week of moderate physical activity or at least 75 min of vigorous physical activity per week
  Strength training exercises at least 2 days per week
  Additional benefits can be seen with increased levels of exercise even beyond 300 min of moderate activity or 150 min of vigorous activity per week, but the most substantial benefit occurs in the former category.
- For children and adolescents aged 6–17 years [1, 5]:
  Aim for a goal of 60 min of moderate or vigorous activity each day
  At least 3 days per week of vigorous aerobic activity, bone strengthening and muscle strengthening activities
- For adults age 65 and older, the abovementioned quantity and intensity of physical activity for applies. Of note, special attention should be paid to focusing on multicomponent activities that include elements of balance training as well as muscle building and aerobic activities [1]. Furthermore, while striving toward the standard exercise goals of 150 min of moderate physical activity is ideal, older adults with chronic medical conditions must consider that modifications might need to be made, and he or she should strive to be as physically active as their abilities and conditions allow. For flexibility, static stretches are encouraged, and activities that do not impose excessive orthopedic stress such as walking, stationary bike, or aquatic exercise should be considered [6].

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Exercise Types/Intensity

Now for the next question: "What kinds of exercise count toward these goals?" To help answer this, let us look at the concept of a MET. MET can be defined as "the metabolic equivalent of a task." 1.0 MET is roughly defined as the rate of energy expended by an individual seated at rest. Table 1 illustrates approximate exercise intensities of some activities expressed in METS.

Of note, it is often difficult to explain the concept of METS in a brief clinic visit, and level of exercise is often more easily explained by discussing judgment of intensity of exercise based on how one feels during the activity. For example, one might be performing an activity in the moderate intensity activity level if breathing is quickened but not out of breath or if one is lightly sweating after about 10 min of the activity. Another clue that an activity falls in the moderate intensity category is the ability to continue to talk but not being able to sing while performing the activity. For vigorous intensity activities, some signs include sweating after a few minutes and being able to only say a few words without pausing the activity.

Sedentary Behavior

More recent research specifically highlights the increases in sedentary activity in recent years, along with the health repercussions of sedentary behavior. Sedentary behavior can be defined as waking behaviors with low energy expenditure less than or equal to 1.5 METS. Examples are sitting, reclining, or lying down. Higher rates of sedentary activity increase the risk of cardiovascular disease, type 2 diabetes, certain cancers (colon, endometrium and lung), and all-cause mortality. While reaching the 150 min per week goal of moderate physical activity has been shown to yield the greatest benefits, reducing sedentary behaviors to any degree has notable health benefits – even 5 min at a time. Family physicians have an opportunity to lead by example as well as to make significant community and national health benefits by adhering to personal exercise habits as well as by leading community initiatives.

Physical Activity Assessment and Exercise Prescriptions

Assessing levels of physical activity of patients can be challenging, but there are tools that can make this more straightforward and useful. One easily incorporated tool is the inclusion of a "Physical Activity Vital Sign" (PAVS) in every visit. By asking the following two questions, one can quickly assess whether or not a patient is meeting exercise goals:

1. On average, how many days per week do you engage in moderate to strenuous exercise like a brisk walk?
2. On average, how many minutes do you engage in exercise at this level?

While the PAVS is geared to adult patients, incorporation of similar questions into pediatric and adolescent visits should be considered. With the pediatric population, consider including questions about total screen time per day, as well as exercise both at school and at home and as a group with family.

One important way that practitioners can promote patient adherence to physical activity recommendations is to write exercise prescriptions [7]. Collaboratively working with patients, exercise

Table 1 Examples of physical activity intensity categories [7]

Intensity level	METS	Examples of activities
Light-intensity activities	<3.0 METS	Walking at a leisurely pace (<2 mph), cooking, light household chores
Moderate-intensity activities	3.0–5.9 METS	Walking briskly, moving the lawn, doubles tennis
Vigorous intensity activities	>6.0 METS	Running, carrying a heavy load upstairs, playing soccer or a basketball game

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plans can be individually crafted to maximize benefit and adherence. The aim is to clearly recommend a level of exercise intensity, duration, and frequency, with a gradual increase toward the patient's eventual personal goal. There are several examples of exercise prescriptions available for review online [7]. Also, in the age of technology, there are numerous devices, apps, and websites that can help patients track exercise habits and goals.

Several other tools are available to help assess readiness to change, explore self-efficacy, identify medical contraindications and other aspects of physical activity. Some include the PAAT, PARmed-X, PAR-Q, and RAPA, and are available online. Of particular interest and utility is ACSM's Guidelines for Exercise Testing and Prescription [8]. A useful algorithm based on ACSM guidelines is freely available online in the "Exercise is Medicine – Healthcare Providers' Action Guide." [5]

Nutrition

Nutrition can be defined as the intake, digestion, and absorption of nutrients to provide energy and support metabolic functions of the body. There is a deeper meaning in nutrition, however, as it relates to the overall functioning of the body, mind, and support of overall well-being. Hippocrates stated, "Let food be thy medicine, and medicine be thy food"; this quote recognizes the critical importance of nutrition and dietary choices in determining the structure and function of the body and mind. Often in today's busy world, the power of nutrition has a tendency to be overlooked. Not only can balanced and mindful nutrition provide overall support to optimal functioning but may play a key role in halting or even reversing many common chronic diseases including hypertension, type 2 diabetes mellitus, and certain cancers such as prostate cancer [9, 10].

The concept of energy balance is the difference between energy intake and energy expenditure, with a negative energy balance leading to the body using energy stores (in the form of fat, protein, and glycogen stores) and a positive energy balance leading to storage of excess energy, mostly as adipose tissue [13]. With rates of obesity consistently on the rise, an important focus of appropriate nutrition is the management of obesity and comorbidities associated with it.

Diet Types

With a multitude of nutrition information flooding the media, it is often difficult to ascertain which types of diets or nutrition advice is most evidence based and most beneficial. Here are some of the most current evidence-based diets and nutrition recommendations:

- Mediterranean Diet [14]
  - Places emphasis on monounsaturated fats from olive oil, fruits, vegetable, whole grains, legumes, nuts, fish, and moderate alcohol consumption
  - Limits red meat, refined grains and sugar
  - Has been shown to reduce rates of diabetes mellitus type 2, certain cancers, cognitive decline with age, cardiovascular disease, and overall mortality
- DASH (Dietary Approaches to Stop Hypertension) Diet [15]
  - The DASH diet places emphasis on increasing the amount of fruits, vegetables, whole grains, and low-fat dairy products.
  - Limits saturated fats, cholesterol, refined grains and sugars, and aims for no more than 2400 mg of dietary sodium per day.
  - Studies show a particular improvement in blood pressure with this diet, and when DASH diet is practiced in conjunction with lowered sodium, blood pressure lowering effects in mild hypertension are on par with antihypertensive medication monotherapy [15]. A combination of the DASH diet and low sodium intake reduced systolic pressure on average by 9 mm Hg, with a smaller decrease in diastolic pressure of 4.5 mm Hg.
  - Also has favorable effects on obesity and diabetes mellitus type 2.
- Whole-Food Plant-Based Diet

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  - Focuses on grains, legumes, nuts, seeds, fruits, vegetables, and plant oils.
  - Limits or avoids meats, eggs, processed carbohydrates and sugars.
  - Has been shown to lead to decreased rates of obesity, diabetes mellitus type 2, hypertension, CVD morality, prevent or slow the growth of certain types of cancer such as prostate [10], reduces the risk of dementia [14], and improvements in overall well-being.
  - This category may overlap with vegetarian diet (avoiding meat but eating some animal products such as dairy or eggs), a vegan diet (avoiding all animal products), or a flexitarian diet (predominantly plant-based foods with occasional animal products).

Of note, there are some commonalities among these three presented categories. Using currently available data, the following points seem to be most supported by evidence and can help with deciding which guidelines to promote and how best to counsel patients [15]:

- Plant-based foods should be emphasized over animal-based foods in the diet.
- Focus on whole foods rather than processed foods.
- Water should be the primary beverage consumed.
- Intensive lifestyle modification to increase activity should be recommended to patients at high risk of cardiovascular disease.
- Free sugars should be limited to less than 10% of daily calories.
- Avoid beverages with processed sugars.
- Limit the daily intake of sodium to no more than 2300 mg per day for adults.
- Be mindful of portion sizes.
- Assess for and address barriers to health behavior change.

Obtaining and preparing nutrient dense foods does take work, but finding ways to incorporate a focus on nutrition into daily routines can optimize both physical and mental health and improve overall well-being.

Nutrition Assessment

To best support a patient's nutrition goals, one must first assess the patient's overall nutritional status and dietary routine. One tool to assist with obtaining a base nutrition assessment is the "ABCD's" of the basic nutrition assessment, with an example outline as follows:

A. : Anthropometric data
   - Height, weight, BMI, waist circumference, sometimes body fat percentage

B. : Biochemical data
   - Lab work and other tests

C. : Clinical assessment
   - Medical history
   - Weight history
   - Activity level
   - Physical exam – vital signs, special attention to signs of nutritional deficiency

D. : Dietary assessment
   - Finding out baseline food intake/dietary patterns/schedule/lifestyle will help the physician provide realistic, individualized goals
   - Basic data collection – 24-Hour Food Recall OR
   - Basic data collection – 3-Day Food Record (2 work days and 1 off day)
   - Needs to be specific (type of food/quantity/measured amount/preparation style/liquid intake)
   - Needs to include timing of food/beverage intake

Nutrition Prescriptions

Just as writing exercise prescriptions can help patients reach their physical activity goals, nutrition prescriptions can help patients reach their dietary goals. When writing nutrition prescriptions, it is helpful to adhere to a consistent format. One example is the "SMART" technique, which is outlined with examples below:

- Specific – select a specific food or category of food (i.e., "eat an apple")

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- Measurable – how many/how much (i.e., "eat one medium apple")
- Accountable – who makes food decisions, who buys the food in the home? What setting does the patient eat in? (i.e., How much control does the patient have over their food choices?)
- Realistic/forgiving – What is available to the patient?
- Time bound – How frequent? For how long? (i.e., "eat one medium apple daily for the next one month")

Nutrition prescriptions can be both positive or negative prescriptions. A positive prescription focuses on foods to add to the diet and a negative prescription focuses on which foods to take away from the diet. In general, positive prescriptions tend to achieve better clinical results and outcomes than do negative prescriptions, but both can be helpful. For example, a positive prescription might look like the example above, i.e., "eat one medium apple per day for the next one week." An example of a negative prescription might place a limit on a particular food or might prescribe to avoid a food altogether. For example, a negative prescription might look like: "cheese, ½ cup, no more than once per week for the next 4 weeks" or "avoid all sodas and sugared beverages for the next 4 weeks."

A Note on Vitamins and Supplements

Many patients often ask the question, "which vitamins or supplements should I be taking?" The answer is unfortunately not straightforward, and there is little evidence to support recommendations for most vitamins or supplement to the greater population. One study evaluated some vitamins and supplements to see if they offered any significant improvement on cardiovascular health or mortality, this was inconclusive [16]. Rather than focusing on promotion of particular supplements, it is likely most beneficial to help patients focus on ways that he or she might improve overall diet, as needed nutrients can generally be obtained from a well-balanced whole food diet.

Some current evidence regarding some of the most common vitamins/supplements:

Multivitamins

- Multivitamins alone have not consistently been shown to improve cardiovascular outcomes or improve mortality risk.

Fish oil

- Particularly omega-3 long-chain polyunsaturated fatty acid (LC-PUFA).
- Might have some benefits, including a lowered risk of myocardial infarction and CAD.
- Studies have not shown consistent significant results with regards to improvement in lab markers such as hemoglobin A1C or lipid panels after fish oil supplementation [17].

Folic acid

- Might have some benefit to overall cardiovascular health such as diminished stroke risk.
- Not particularly beneficial in the United States as many foods are already fortified with folic acid, but studies did show greater benefit in countries where food supplementation (mostly grains and processed foods) is not commonplace.
- Supplementation of folate is recommended for women of childbearing age who are pregnant, are planning, or may become pregnant. To prevent neural tube defects in fetuses of women at average risk, a supplement containing 400–800 μg of folic acid daily is recommended per the USPSTF [18].

Vitamin D

- There is inconsistent evidence to support supplementation of vitamin D for improvement of bone health, cardiovascular health, prevention of cancer, all-cause mortality, or improved pregnancy outcomes [19, 20].
- Thus, routine vitamin D supplementation in community dwelling adults is not recommended.
- There is insufficient evidence to recommend screening the general population for vitamin D deficiency.
- Treating asymptomatic adult individuals with identified deficiency has not shown improvements in health.

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- The United States Preventative Services Task Force (USPSTF) recommends against supplemental vitamin D to prevent falls in community-dwelling adults aged 65 years or older [21].
- One population where there are clear indications for vitamin D supplementation are breastfeeding newborns. The AAFP recommends that breastfed infants receive 400 IU of vitamin D supplementation soon after birth until age 1 year. This recommendation applies to both exclusively and partially breastfed infants.

Calcium

- Similar to vitamin D, there is insufficient evidence to show improved outcomes from calcium supplementation, and supplementation should generally be avoided in the adult population.
- Some studies have even suggested a possible increase in stroke risk when taking calcium and vitamin D concurrently, but these data are inconclusive [21].

Vitamin E

- The USPSTF specifically advises against supplementation with vitamin E for primary prevention of cardiovascular disease or the prevention of cancer [16].

Vitamin B12

- Screening people at average risk for vitamin B12 deficiency is not recommended [22].
- Screening should be considered for patients at risk of B12 deficiency including patients who have a history of bariatric surgery, patients on long-term PPI or H2 blockers or Metformin, and those who follow a strict vegan diet.
- Patients who have had bariatric surgery should receive 1 mg of Vitamin B12 PO daily indefinitely.

Motivational Interviewing

Motivational interviewing (MI) was developed by Miller and Rollnick as a method to address intrinsic motivation for changing behaviors by exploring and addressing ambivalence [25]. MI has been applied to various populations and concerns in health care [29]. MI as a counseling style has been used in health care to enhance a person's intrinsic motivation for change and adherence to treatment [26].

MI has been supported empirically and is consistent with theories of intrinsic motivation [27], [28]. Further research has demonstrated that these techniques of MI improve the quality of the clinician-patient interaction. MI can help clinicians integrate evidence-based medicine with patient-centered care and shared decision-making. Family physicians are uniquely placed to integrate these techniques to assist with prevention, health promotion, and wellness [29].

In primary care, MI is often more commonly used in situations where the patient demonstrates ambivalence and the health care provider is assisting with the addressing that uncertainty, e.g., lifestyle choices, adherence to medications, or engagement in treatment recommendations [30]. Motivational interviewing involves four steps: engaging, focusing, evoking, and planning (Fig. 1). These steps are basic building blocks that can be used in any encounter with a patient-centered focus. Engaging is where the clinician works towards building a mutual helping relationship. Focusing is creating a specific guide and plan about change. Evoking is a vital component as this is where eliciting the patient's own reasons



Fig. 1 Four steps of motivational interviewing

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for change are highlighted. Planning is the step in which there is a tangible attainable plan of action made, with an ongoing commitment to changing the identified behavior.

When using MI, it is important to listen carefully with the goal of understanding the person's challenge with making changes. This technique is not about giving advice but rather asking pointed questions to help understand the person's barriers and interest to change. Some example questions may include:

- Why would you want to make this change?
- How might you go about it in order to succeed?
- What are the two best reasons to do it?

By listening intently, the person's readiness to change will also become apparent. The Transtheoretical Model (also called the Stages of Change Model), developed by Prochaska and DiClemente in the late 1970s, focuses on the decision-making of an individual regarding change [31]. The foundation of the Transtheoretical Model (TTM) is the assumption that people do not change behaviors quickly and often it is a process of decision making. This framework highlights that a person will change through a cyclical process and there are various factors that influence one's passage through those stages [31, 32]. This theory has five stages as used in health care (Table 2).

This framework is often not static, a person's readiness to change and individual change processes can be fluid. While there are outcomes specific to the stage, in practice can be often seen is a person vacillating between the stages based on aspects of the task at hand to change. For example, when if a health care provider is working with someone on changing habits for weight loss, a patient may be in the action stage regarding physical activity but be in the contemplation stage with removing fatty foods from their eating habits. By utilizing the techniques of MI and patient-centered communication skills, a health care provider can enhance preventative behaviors for health and well-being.

Stress Management

Stress has been called the most prevalent disease of modern society: an epidemic brought about by the pace of modern life and the pressure to succeed in a climate of increasing job insecurity [33].

In 2018, a large national study in the United Kingdom reported that three-quarters of the study participants had been so stressed in the past year that they had felt overwhelmed or unable to cope. One in three of these people had been left feeling suicidal, and one in six had self-harmed [36].

Social and political factors, that may include finances, the economy, family responsibilities, and relationships, have been reported to be the top causes of stress among Americans. This stress affects every aspect of people's lives. Stress, poor lifestyle choices, and disease symptoms often coexist and may exacerbate each other. Headaches, muscles tension and pain, fatigue, changes in sex drive, stomach upset, and sleep problems are often encountered. Stress can affect the mood

Table 2 Transtheoretical Model (TTM) Stages of Change

Precontemplation	There is no intention to change behavior. The person may acknowledge interest in the desired outcome but does not demonstrate willingness to make the necessary steps
Contemplation	The individual is beginning to consider change at some indeterminate time in the future. The timeframe is sometimes defined as a goal in about the next 6 months
Preparation	The person is planning to change in the immediate future (approximately in the next month). They may engage in change talk and making plans for the change.
Action	Here the individual engages in behavior change. An ongoing state of behavior change.
Maintenance	The person is sustaining the change (often defined as longer than 6 months). At times the behavior is modified as the individual may experience/learn to reframe challenges in continuing with the new behavior.

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with increases in anxiety, restlessness, lack of motivation and focus, feelings of being overwhelmed, irritability, sadness, and depression. It can also affect behaviors such as over- and undereating, angry outbursts, drug and alcohol misuse, social withdrawal, and decreased exercise [35].

It has been shown that simply talking about stress management with patients can help to reduce the effect that it can have on a person's overall health. An easy tool for primary care providers to use to try and identify stress in patients is the prime-MD patient health questionnaire (PHQ) which has been validated to identify mental health disorders [36]. It allows the physician to quickly evaluate a patient's stress, so this can be investigated further if necessary. According to the American Psychological Association, 32% of Americans believe that it is extremely important for health care providers to discuss stress management, but only 17% report that they have discussed stress management with their physicians [35].

Meditation is one technique that has been shown to be effective in decreasing stress in otherwise healthy individuals [37, 38]. Mindfulness meditation has been shown to result in positive changes in the brain and immune function [39]. There is evidence that mindfulness meditation programs may alleviate anxiety, depression, and pain, and they may reduce stress, distress, and improve the quality of life among patients with chronic disease or mental health diseases [40].

It is imperative that primary care physicians not only help to recognize stress in their patient's but also start a conversation about a team-based approach to managing it. Online-based mindfulness strategies have been shown to be modestly effective in reducing overall stress, anxiety, and depression. Given its wide reach, low cost, and easy access, online-based mindfulness strategies are recommended as a part of an overall stress reduction treatment regimen [41]. There are also mindfulness-based stress reduction workbooks with strategies for reducing stress and ways to incorporate mindfulness into daily life that may be very beneficial to both patients and health care practitioners.

Tobacco Cessation

According to the CDC, cigarette smoking is the leading cause of preventable disease and death in the United States, with almost 14% of adults currently smoking cigarettes [42]. Cigarette smoking alone accounts for about one out of every five deaths every year. In addition to the significant health burden that smoking presents, it also has a significant economic burden with more than $300 billion each year lost to smoking-related illness in the form of direct medical care costs and lost productivity dollars. Encouraging smoking cessation can be one of the most beneficial things we can do for our patients and tobacco use should be assessed at all clinical encounters. In fact, most cigarette smokers would like to quit smoking [44]. Some options for encouraging consistent screening are: incorporating a screening question to ask about tobacco product use into the rooming process, or/and including a question in provider note templates to monitor tobacco use every visit as a health "vital sign." Of note, tobacco products such as chewing tobacco and vaporizers or electronic cigarettes also have significant health risks and are included in this discussion as a focus on cessation of all nicotine containing products. Tobacco use is the top preventable cause of death in the United States [45]. Motivational interviewing tools can be extremely helpful with bringing up the topic of tobacco cessation and gauging a patient's readiness for change.

Alcohol Consumption

According to the 2018 National Survey on Drug Use and Health (NSDUH), 70% of people ages 18 or older reported that they drank alcohol in the past year, and 26.45% of people 18 or older reported binge drinking in the past month [45]. When looking at the statistic of 88,000 deaths per year in the United States from an alcohol-related cause, alcohol is the third leading preventable cause of death. From these statistics, it is easy to see that alcohol consumption is something that every primary care physician needs to have a conversation with their patients about, and

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why the USPSTF recommends screening all adults for unhealthy alcohol use. Furthermore, studies have shown that physicians often fail to identify or adequately address patients' drinking habits [47].

Alcohol Use Screening

Recognizing who may be high risk by using validated screening tools is one way to incorporate consistent screening into your patients' care. To adequately assess alcohol use, it is important to understand standard serving sizes of alcoholic beverages and recommended limits of alcohol use. One drink equates to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor (one shot). The National Institute on Alcohol Abuse and Alcoholism recommends limiting alcohol as follows:

- Men younger than 65 years old:
  - No more than 2 drinks per day
  - *And* no more than 14 drinks per week
- Women of any age and men 65 years and older:
  - No more than 1 drink per day
  - *And* no more than 7 drinks per week

There are numerous tools that a health care provider can use to identify excessive alcohol consumption. The AUDIT screening questionnaire is one example of a helpful screening tool that has been validated to be a good predictor of alcohol-related social and medical problems. It can be used to objectively ask ten questions about alcohol intake to identify patients who may be drinking more than what is recommended. A briefer version of the questionnaire is the AUDIT-C, which includes the first three questions from the full AUDIT questionnaire. Studies have shown the AUDIT-C to be almost as effective as the AUDIT and is often preferred in busy clinical settings due to its brevity [48].

AUDIT-C:

- Question 1: How often did you have a drink containing alcohol in the past year?
  - Never (0 points)
  - Monthly or less (1 point)
  - Two to four times a month (2 points)
  - Two to three times per week (3 points)
  - Four or more times a week (4 points)
- Question 2: How many drinks containing alcohol did you have on a typical day when you were drinking in the past year?
  - 0 to 2 (0 points)
  - 3 or 4 (1 point)
  - 5 or 6 (2 points)
  - 7 to 9 (3 points)
  - 10 or more (4 points)
- Questions 3: How often did you have six or more drinks on one occasion in the past year?
  - Never (0 points)
  - Less than monthly (1 point)
  - Monthly (2 points)
  - Weekly (3 points)
  - Daily or almost daily (4 points)

Scores of $\geq$4 for men or $\geq$3 for women indicate a positive screen. A positive screen indicates an increased risk of alcohol misuse.

When the risk of unhealthy drinking is identified, it is important for the health care provider to counsel the patient and assist with development of a plan to address the issue. A brief alcohol intervention is beneficial, and interestingly, even 5 min of advice has been shown to be as effective as 20 min [49]. During counseling, it can be helpful to engage a patient in behavior change by asking the patient's permission to discuss, then listening to their thoughts and using reflection. Several helpful resources can be found online, one of which being the NIAAA website's publication entitled "Helping Patients Who Drink Too Much." [50] It includes information about screening and managing the care of patients who consume more alcohol than recommended in a primary care setting.

Importance of Well-Being to the Health Care Professional

Of important mention to family medicine practitioners, taking time to prioritize personal health is essential. Optimizing physical activity habits and

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personal nutrition can yield a multitude of personal benefits as well as leading by example to patients and our communities. In addition to optimizing nutrition and exercise, a focus on personal rest and adequate sleep, stress management, and avoiding tobacco and excess alcohol can provide a multitude of personal benefits.

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Health Care of the International Traveler

8

Timothy Herrick

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Introduction

The number of travelers crossing borders each year continues to rise. According to the World Tourism Organization, the number of travelers crossing international borders exceeded 1.4 billion in 2020 [1]. Currently, fewer than half of all international travelers seek a travel consultation prior to departure [2]. A basic understanding of traveler's health is necessary to provide travel advice to patients, as family physicians often bridge the gap between knowledge of a patient's health history and travel medicine. In a recent study, primary care providers were second only to the Internet in patient-identified sources of travel health advice [2].

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Pre-Trip Consultation

A pre-trip consultation is recommended at least 4 to 6 weeks prior to departure. The components of the consultation are history intake, review of routine vaccinations, travel-related vaccinations, traveler's diarrhea treatment and prophylaxis, malaria prophylaxis, review of personal protective measures, altitude illness prophylaxis, and safety and accident prevention.

History Intake

This includes the traveler's pertinent medical history, current medications, and allergies, which may affect choices for both travel-related medications and vaccinations. Anticipatory guidance for chronic conditions such as diabetes, heart disease, asplenism, and immune compromise may also need to be addressed. Vaccination history is also relevant, as live vaccines must be given either simultaneously or 28 days apart. Several important travel-related questions are also pertinent, including purpose of travel, specific locations that will be visited in the destination country or countries, accommodations, and traveler habits.

Routine Vaccinations

The travel visit also presents an opportunity to catch up on routine vaccinations. These may include pneumococcal vaccination, Tdap, herpes zoster vaccine, and flu shots. Especially important to verify are MMR and varicella immunity, as immunity is pertinent for travel to parts of the world where disease burden for these illnesses is relatively high. A second MMR is recommended for many endemic countries for adults who can only have a single documented vaccination during childhood or later.

Travel-Related Vaccinations

Hepatitis A

Hepatitis A is transmitted through fecal-oral contamination. Its prevalence in developing countries is often high, and vaccination is recommended for all destinations in these areas. The illness rarely causes death but morbidity is significant. Severity of illness is variable between age groups; the illness tends to be more severe in adults.

Hepatitis A is a 2-dose vaccine series, with each dose separated by at least 6 months. It is licensed for use in patients 1 year and older and is safe for use in pregnant women. The first hepatitis A shot imparts >90% immunity and, in healthy travelers under 40 years old, can be given at any time prior to departure [3]. In older or immunocompromised travelers, it is recommended that at least one hepatitis A dose be given at least 2 weeks prior to departure to generate adequate immunity [3]. Once both doses are given, immunity is considered lifelong for hepatitis A and no further boosters are needed.

Hepatitis A vaccine also exists in a 3-dose series called Twinrix, where it is combined with a hepatitis B vaccine. Only persons aged 18 and older are eligible to receive the Twinrix vaccine. The vaccine is administered at 0, 1, and 6 months. It is important to note that immunity imparted with each Twinrix shot is less than the individual hepatitis vaccines administered separately. For adequate immunity (>95%), two doses of Twinrix are recommended prior to travel [7].

In children less than 1 year old, hepatitis A immunoglobulin (Ig) is available; however, this age group tends to have controlled diets which may reduce hepatitis A risk. There are also conflicting recommendations for hepatitis A Ig use for pretravel prophylaxis [3, 7]. The availability and cost of hepatitis A Ig can also be a challenge; therefore, these considerations should be taken into account.

Hepatitis B

Hepatitis B is transmitted through contact with infected blood or bodily fluid products. Several factors increase the risk of hepatitis B. These include volunteer work in which contact with blood or bodily fluids might be encountered (e.g., medical volunteer projects) as well as the potential for sexual contact. An injury or illness while abroad which leads to local medical care may also increase risk of exposure to hepatitis

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B. Traveler risk factors should be assessed prior to administration of hepatitis B vaccination.

Hepatitis B vaccine exists in a 3-shot series spaced at least 0, 1, and 6 months apart. It is licensed for use starting at birth and is safe for use in pregnancy. One dose of hepatitis B imparts approximately 30 to 55% immunity, 2 doses 75% immunity, and 3 doses >95% immunity in adults [4]. At least 2 doses of hepatitis B are recommended prior to travel. It is important to note that the immune response to hepatitis B decreases with age; after age 40, protective immunity from full hepatitis B vaccination decreases to below 90% and to 75% by age 60 [4]. Immune suppression can also decrease the response to hepatitis B vaccination. Therefore, for some at-risk travelers, there may be a benefit in checking hepatitis B antibody titers prior to travel.

A new vaccine, based on a novel adjuvant, known as HepB-CpG was licensed in 2018. It could have application in travel in that it is fully immunizing after 2 doses spaced 4 weeks apart.

Typhoid

Typhoid fever indicates an infection by *Salmonella typhi*, which is spread by fecal-oral transmission. *S. paratyphi* can also cause a similar clinical illness.

There are currently two licensed vaccines in the United States. Typhim Vi is a polysaccharide subunit vaccine, given intramuscularly, with an effectiveness of 55–75%. A booster for ongoing exposure is needed after 2 years. Oral typhoid vaccine consists of a live attenuated strain, Ty21a, which confers similar protection. Unlike the polysaccharide vaccine, however, studies have shown that the oral vaccine does confer some protection against paratyphoid [5]. The manufacturer's instructions are for 1 capsule to be taken an hour before eating every 48 h for 4 doses. The capsules require refrigeration, and revaccination is recommended every 5 years. It can be administered concurrently or at any time in relationship with other live viral vaccines (i.e., yellow fever). However, as antibiotics can impact the vaccine's immunogenicity, it is recommended that no antibiotics be given with, or 3 days before or after, the vaccine. In the case of proguanil, which is one of the active components of the antimalarial atovaquone/proguanil (Malarone ®), a 10-day interval should be maintained between completing the oral typhoid vaccine and starting proguanil. Coadministration with mefloquine is not problematic. As no vaccine confers complete protection, attention to hygiene and eating practices should be emphasized in all travelers.

Yellow Fever

Yellow fever has a widespread distribution in Africa, Panama, and parts of South America. Though classified a hemorrhagic fever, liver and kidney injury is responsible for its morbidity and mortality.

There is a safe and effective vaccine based on an attenuated strain, 17D. Many countries mandate vaccination of travelers. Some countries may even require vaccination of travelers who will transit in airports. Vaccination is restricted to certified vaccination centers. Vaccinees should be provided the International Certificate of Vaccination (yellow card) correctly filled out. Travelers should be told to keep this card with their passport as generally it must be displayed before passport control.

The WHO stated in 2013 that a single yellow fever immunization confers lifelong immunity [6]. While yellow fever vaccine is generally safe, as a live vaccine, it is contraindicated for the immunosuppressed and generally is avoided in pregnant and lactating women. In addition, there are visceral and neurological reactions which occur more frequently at the extremes of age. Therefore, yellow fever is relatively contraindicated less than 9 months of age and absolutely contraindicated below 6 months of age. There is a relative contraindication over age 60 as well, as adverse reactions, though still rare, are increasingly common above this age [7].

Those travelers who have a contraindication to yellow fever vaccination, including age, should be provided an exemption card certifying the medical reason for not receiving the vaccine. The exemption section is included in the International Certificate of Vaccination (yellow card).

Polio

The eradication of polio worldwide has proven to be an elusive goal. At present there are

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10 countries in the world that are considered either polio infected or polio exporting. This list evolves rapidly, but those countries affected and recommendations for polio vaccination are listed and maintained on the CDC website (www.cdc.gov). All travelers to countries with polio should have completed the standard series. In addition to this, adults whose polio vaccinations took place in the remote past should have a single, lifetime polio booster. Long-term (more than 4 weeks) travelers to certain high-risk countries may be required to show proof of vaccination within 1 year for entry and exit. Up-to-date information is available from the WHO [8].

Meningococcus

Infections due to *Neisseria meningitidis* occur worldwide. In the United States, quadrivalent meningococcal vaccine (MCV4) is part of the routine vaccination program. There are two destinations for which vaccination is required or recommended: The *Hajj*, the pilgrimage to Mecca in Saudi Arabia, and the meningitis belt of sub-Saharan Africa. In the meningitis belt in Africa, meningitis can occur at any time but is more frequent during the dry season, from December to June. The serotype of greatest concern is group A.

Vaccination should be considered for all travelers to areas within the meningitis belt if their travel will extend within a month of the December to June window. Quadrivalent conjugated vaccine is the only vaccine presently available for all travelers aged 2 month and older, including those over 55. Boosters are required every 5 years should the traveler remain at risk. Adolescents and preadolescents already vaccinated will not need additional boosters for travel.

Vaccination against type B meningococcus is not needed for travel.

Japanese Encephalitis

Japanese encephalitis (JE) is a mosquito-borne illness prevalent in areas of Asia. Its overall prevalence is 1 case per one million travelers [9]. The risk of contracting the illness includes travel lasting 1 month or greater in rural areas or itineraries in at-risk destinations, which include prolonged and extensive outdoor activities. Symptoms of the disease include change in mental status, fever, and seizures. The fatality rate is 20–30% [9]. Long-term neurological and psychiatric sequelae are seen in 30–50% of survivors [9].

Several brands of Japanese encephalitis vaccine exist in different parts of the world. The current vaccination in use in the United States is IXIARO. IXIARO is a 2-dose vaccination, with doses ideally separated by 28 days, although the second dose can be given one after the first, and ideally at least 1 week prior to travel. The first dose imparts approximately 41% immunity, while the second dose leads to 97% immunity [10]. In addition to use in adults, the IXIARO vaccine has now been approved for use in children aged 2 months to 16 years as of May 2013.

Boosters for JE vaccination are recommended in 1 year for adults, if repeat travel to affected areas is planned. Further booster dosing in the pediatric population is still being actively studied.

Rabies

Rabies unfortunately is almost always a fatal illness. The most common transmission occurs through a bite with an infected animal. Worldwide, the most common source of rabies is infected dogs [11]. Children are particularly prone to rabies exposure while traveling, as they are less likely than adults to exercise caution when coming into contact with animals.

Pretravel vaccination against rabies is recommended for travelers who are visiting locations with high animal rates of rabies and inadequate access to rabies treatment [12]. In many locations in developing countries, access to rabies immunoglobulin (Ig) might not be readily available. Pretravel rabies vaccination would preclude the need for rabies Ig post-exposure in these locales. Vaccination can also be considered for travelers who plan on visiting rabies-endemic locations for extended periods of time (longer than 1 month). Vaccination is often quite expensive and consists of a 3-dose series at days 0, 7, and 21 (or 28). It is licensed for use in persons of all ages and is safe for use in pregnant women.

Post-exposure treatment is 3-pronged [12], consisting of wound care, administration of the

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Table 1 Post-exposure treatment of rabies [12]

Received pre-exposure vaccination?	Wound cleansing needed?	Rabies immunoglobulin administration needed?	Post-exposure immunization schedule
Yes	Yes	No	Days 0 and 3
No	Yes	Yes	Days 0, 3, 7, 14

rabies immunoglobulin (if no pre-exposure vaccination was given), and postexposure vaccination. See Table 1 for postexposure treatment.

Boosters for rabies are generally not recommended for most travelers on subsequent trips where exposure to rabies may be significant [12]. Exceptions to this are travelers who may be working in a veterinary capacity or research capacity with wildlife, where it is recommended that serum antibody titers for rabies be checked prior to revaccination.

Traveler's Diarrhea Prophylaxis

Traveler's diarrhea is a common cause of infectious illness while abroad, affecting an estimated 30–70% of travelers [13]. It is defined as three or more episodes of diarrhea in 24 h with at least 1 of the following associated symptoms: fever, nausea, vomiting, abdominal cramps, tenesmus, or bloody stools. Traveler's diarrhea causes significant morbidity, as it leads to significant disruption in traveler activities and itineraries due to symptoms. While adventure travel and avoidance of precautions put a traveler at higher risk, traveler's diarrhea is also reported on luxury travel itineraries as well.

The most common cause of traveler's diarrhea worldwide is enterotoxigenic *Escherichia coli* [13]. On the rise is enteroaggregative *E. coli* as a pathogen. Other pathogens include *Campylobacter*, *Salmonella*, *Shigella*, viral pathogens, and protozoa such as *Giardia*.

Empiric treatment for traveler's diarrhea is guided by balancing likely pathogens, local resistance patterns, and likely side effects. Ciprofloxacin has been the most common antibiotic used to treat traveler's diarrhea in adults, but concerns about resistance patterns and possible side effects have limited its usefulness. Azithromycin is generally considered the preferred agent. It is given as 500 mg daily for 3 days for adults, and 10 mg/kg per day for 3 days for children. Ciprofloxacin may be used in cases of personal preference or in situations where there are drug compatibility problems due to its hepatic metabolism. Azithromycin is the treatment of choice for both pregnant women and children. Many clinicians prescribe treatment doses of antibiotics for traveler's diarrhea for each traveler to fill in advance and take with them on their trips.

Concurrent treatment of traveler's diarrhea with both loperamide and antibiotics has been shown to decrease traveler's diarrhea symptoms more rapidly than either treatment option alone [14]. A recent meta-analysis of traveler's diarrhea in several communities around the world showed increased likelihood of clinical cure at 24 h and 48 h if combination loperamide/antibiotic therapy is given [14].

Prophylaxis for traveler's diarrhea is a controversial topic. The first-line measure of "boil it, cook it, peel it, or forget it" should be reviewed with all travelers. Drinking water that is bottled or boiled at a rolling boil for 1 min to kill potential pathogens is advisable in all at risk locations. The CDC currently does not recommend traveler's diarrhea prophylaxis [13] due to the development of possible antibiotic resistance. It should be noted, however, that prophylaxis is very effective and can be considered for those with risk factors such as inflammatory bowel disease. Options for prophylaxis include quinolones, which can reduce incidence of diarrhea by up to 90% [13]. Rifaximin is limited by expense but is another option for traveler's diarrhea prophylaxis. Daily bismuth subsalicylate (Pepto-Bismol®), an option that is not available to pregnant women or children due to its aspirin component, reduces incidence of diarrhea around 50% [13], though the patient should be warned of black stools.

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Lactobacillus is also a popular prophylactic option, though studies regarding its use in traveler's diarrhea prophylaxis are inconclusive [13].

Malaria Prophylaxis

The WHO reported for 2018 an estimated 228 million cases of malaria with 405,000 deaths, most of which are in children in sub-Saharan Africa [15]. Malaria in travelers is potentially lethal, but avoidable. In 2016, there were 2078 cases reported in the United States and 7 deaths, almost all in travelers [16].

Historically, four species, *Plasmodium falciparum*, *P. ovale*, *P. malariae*, and *P. vivax*, caused human disease. A fifth species, *Plasmodium knowlesi*, a primate species, now causes significant human disease in Southeast Asia, with a dozen American cases reported in travelers through 2013 [17] as well as many European cases [18]. While all species contribute to human morbidity, the burden of mortality is due to *P. falciparum.* While resistance patterns vary, in general, prophylaxis and treatment that effectively target *P. falciparum* in a given area will be effective against the other forms of malaria as well.

Individuals exposed to malaria on an ongoing basis often develop a partial immunological protection called premunition. This protection allows a low level of chronic infection but generally does not allow the malaria to develop into clinical illness. Anyone who has been outside a malarious area for over 2 years generally has the same risk as a nonimmune individual, though the precise rate of decay of immunity is unclear.

The best measures against malaria are mosquito avoidance, including application of DEET to the skin, bed nets, and clothing, and taking an approved medication for chemical prophylaxis [19]. There are currently several antimalarials recommended for prophylaxis, discussed below.

Mefloquine

Mefloquine has been widely used for several decades. It is somewhat controversial, with common minor side effects such as vivid dreams and disturbed sleep and rare adverse cardiac and psychiatric effects. Avoidance of this drug in patients with known cardiac problems, especially those who take QT interval prolonging medications, is recommended. Those who have or have had a psychiatric diagnosis, including depression, should use another agent. It is helpful to begin mefloquine prophylaxis 2 weeks prior to travel instead of the traditionally prescribed 1 week prior. This both allows for a period of time to evaluate the development of any side effects and achieves a drug-steady state prior to arrival. Mefloquine should continue to be taken 4 weeks after leaving the malarious area. Areas of increasing resistance have made this drug less useful for much of Southeast Asia [20].

Doxycycline

Doxycycline is useful and effective for malaria prophylaxis. It should be started 2 days prior to travel, taken daily and continued daily for 4 weeks after leaving the malarious area. It is contraindicated in children under 8 years of age and in pregnant and lactating women. Dairy products should be avoided for 2–3-h window before and after ingesting doxycycline. Doxycycline is helpful to take with food to reduce nausea. Photosensitivity has been reported but is not as frequent a problem as with tetracycline. Candida infections can be seen, at times even in men. Interference with oral contraceptives does not seem to be the problem it was once thought to be. However, as with other antibiotics, those taking warfarin should have their dose monitored while on doxycycline.

Malarone

Atovaquone/proguanil (Malarone®) is generally regarded as the best tolerated and most effective of available antimalarials for prophylaxis. There are very few side effects. It is taken daily, 2 days prior to, during, and only 7 days after travel in a malarious area, making this the shortest "tail." Its main disadvantage is cost.

Primaquine

Primaquine is indicated for presumptive antirelapse treatment (PART), previously known as "terminal prophylaxis." Terminal prophylaxis

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with primaquine, at a dose of 30 mg [52.6 mg of salt] per day for 14 days [21], is recommended to all who visit areas where *P. vivax* is present. Primaquine is capable of eliminating dormant malarial hypnozoites in the liver, thereby reducing the frequency of relapse. Primaquine triggers a hemolysis in those with G6PD deficiency, so quantitative testing of this enzyme must be performed prior to prescribing this drug. Primaquine should not be prescribed to pregnant women.

Tafenoquine

Tafenoquine, an 8-aminoquinoline like primaquine, was approved in 2018 for prophylaxis of all species of plasmodium, as well for radical cure of vivax [22]. Because of its long half-life, it is possible to give 200 mg daily for 3 days pretravel, then weekly while at risk, and again 1 week after the risk ends. As with primaquine, it is not to be given to those who have not had a quantitative test ruling out G6PD deficiency, or to pregnant women.

Personal Protective Measures

Insect avoidance is an important component of prevention for travelers to the tropics. Medical prophylaxis for malaria works better in combination with avoidance to lessen the parasite exposure. Other protozoal diseases that are transmitted by insects, such as leishmaniasis and trypanosomiasis, have available treatments but are extremely onerous, making prevention strategic. Viral diseases, such as Japanese encephalitis and tick-bourne encephalitis are preventable by vaccination, but the cost and availability of vaccines may discourage their use, especially in short-term travelers. In addition, viral diseases such as dengue, chikungunya, and zika have no treatment or vaccine yet available, so protective measures are the only prevention. Scrub typhus and many other rickettsial diseases may be treated, but are largely preventable.

In areas of risk, permethrin-impregnated bed nets are a major element in malaria prevention. Travelers should take advantage of these when available. Permethrin is also available as a spray-on product for the treatment of clothes [19], which is strategic for many arthropod-borne illnesses, in particular scrub typhus in Asia and tick-bourne typhus in Europe.

DEET (*N*, *N*-diethyl-meta-toluamide) is a repellent with a long history of safe use. Adverse effects are rare. However, it is best to use clothing that covers much of the body so that DEET can be applied sparingly. The American Academy of Pediatrics recommends 10–30% strength for children older than 2 months of age. Picaridin is a product that can be used as well.

Trypanosomiasis is a rare disease in travelers, but there have been reported cases from those going on game drives. Long sleeves and pants and permethrin treatment are helpful strategies for avoidance. In addition, given that tsetse fly traps are purposefully made in royal blue and black colors to attract the flies, these are good clothing colors to avoid during such activities.

Schistosomiasis is one of the most common diseases of returned travelers. There are several species of this fluke, which in its larval stage is an infection of freshwater snails. Travelers to the tropics should be counseled against swimming in freshwater. Wading and even dangling a body part in the water can also transmit the fluke, as well as bathing with untreated lake or river water.

Certain preventive strategies are difficult to apply to those at highest risk: children under the age of 1, pregnant women, and the immunocompromised. For such travelers, it is helpful to encourage thoughtful reflection as to the risks and benefits of travel. In some cases, travel plans can be modified in such a way that the risk can be mitigated.

Altitude Illness Prophylaxis

In several destinations in the world, altitude illness and prevention become a concern. Symptoms of altitude illness include headache, insomnia, nausea, fatigue, and dizziness. Severity of altitude illness can range from acute mountain sickness which is mild to more serious complications such as high-altitude cerebral edema

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(HACE) and high-altitude pulmonary edema (HAPE).

A discussion of altitude prophylaxis is recommended for destinations that involve overnighting above 2,500 m [23]. The most widely accepted preventive measure is slow ascent [23]. Several medications are available for altitude prophylaxis, including acetazolamide and dexamethasone. Recommended dosing for acetazolamide is 125 mg by mouth twice per day, to start 2 days prior to ascent and to continue until the traveler has acclimatized at their maximum altitude (generally 48–72 h) [23]. Acetazolamide can cause side effects such as diuresis and paresthesia and cannot be used in patients with sulfa allergies. Dexamethasone is a second-line prophylactic option, but as it does not aid in acclimation, it can cause rebound symptoms of acute mountain sickness once stopped. Local herbal remedies are also popular and available in high-altitude destinations worldwide, but efficacy in preventing altitude illness is unproven in studies [23]. The most effective treatment for altitude illness is descent.

Safety and Accident Prevention

A significant proportion of the pretravel visit is dedicated toward the discussion of pre-trip immunizations, malaria, and traveler's diarrhea. However, the primary cause of death among travelers is accidents, such as motor vehicle accidents and falls [24]. For this reason, the topic of safety and accident prevention deserves specific mention during the pre-trip consultation. Depending on the destination, standards and safety for driving can vary significantly. There may be political or civil unrest occurring in various destinations that a traveler should be aware of. Registering an international trip with the US State Department and consulting their website may be helpful in trip preparation.

Sexually transmitted diseases are a risk for travelers who might consider having sex while abroad. Assessing for the likelihood of this during the pre-trip consultation is important, and these travelers should be reminded of both the incidence of STDs in their destinations and the use of barrier protection. There can be variability in the quality of condoms purchased abroad.

Finally, trip and evacuation insurance should be considered prior to departure. This might be most useful for those travelers abroad for an extended period of time, especially in remote locations or for travelers who have one or more chronic illnesses.

Emerging Diseases

In the years prior to this edition, the world has dealt with multiple global infections including Zika, MERS-CoV, and COVID-19. Each of these has had impact on travel, whether regional or global, and temporary or long-term. It is not known now what the impact of these viruses or other as yet unidentified viruses will be on travel planning at a future time when the reader reads these words. The best advice is to survey excellent electronic resources such as the CDC's yellow book, the National Health Service UK's "Travel Health Pro" website, and www.promedmail.org, which relies on observers on the ground to give real-time updates of local epidemiological conditions.

Post-Trip Consultation

The goal of the pretravel consultation is the avoidance of illness during and after travel. There will be times when such measures fail. The likelihood of illness is negatively correlated with preventive measures taken. Pathologies frequently encountered in returned travelers include fever, gastrointestinal disease, skin disease, eosinophilia, and latent tuberculosis.

Fever in Returned Traveler

For purposes of this discussion, fever will be defined as an oral temperature $>$ 100.0 °F, although given the cyclical nature of many fevers, subjective reports of fever should be taken seriously. Even remotely completed travel can cause

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illness, but the large proportion of fever cases present within weeks to months of return from travel. One exception is non-*falciparum* malaria, which can incubate for up to a year, and delayed relapse can occur many years later [25].

The most critical subgroups of febrile returned travelers are those with hemorrhagic symptoms. All patients with fever and hemorrhage who have returned within 21 days from travel should be considered to have a viral hemorrhagic fever and placed in isolation (contact, droplet, and aerosol) until proven otherwise. Not all of these diseases are contagious, but until a specific identification has been made, high transmissibility should be assumed.

The next most important task in the care of returned travelers is to identify potential cases of malaria. In many cases, malaria is the most important cause of fever in a returned traveler [26], and the risk of mortality from this pathogen in non-immune patients makes its rapid identification and treatment critical. Malaria can be contracted in any tropical continent and is the most frequent cause of fever in those traveling from Africa. Dengue is the most frequently encountered pathogen from Southeast Asia, and enteric fever (typhoid) is the most frequently encountered fever from the Indian subcontinent [27]. Other important causes of fever include schistosomiasis, leptospirosis, amebic abscess, tuberculosis, and sexually transmissible diseases, including HIV.

Workup for fever should include a careful history, including the itinerary, associated symptoms, and a physical exam emphasizing ENT, pulmonary, GI, neurological, and integumentary systems. A lab workup including a CBC with differential, thin, and thick smears for malaria and blood cultures can also be helpful. For clinical situations such as dengue or chikungunya, specific viral serologies can also be considered.

In practice settings where results are likely to be delayed, empiric treatment with an antimalarial should be strongly considered. Atovaquone/proguanil is widely available as a prophylactic and is effective as a treatment as well. The same can be said for mefloquine. A more ideal medication artemether-lumefantrine (Coartem) is preferred as a treatment and avoids the theoretical problem of using a medication as treatment that may have failed as a prophylactic agent. For severe malaria, of which there are around 300 cases annually in the US, the drug of choice is parenteral artesunate, which had only been available directly from the CDC but has now received FDA authorization and will soon be available for hospital pharmacies to stock [28]. Quinine has a long-track record, but its potential for arrhythmias limits its utility and it is no longer available in parenteral form in the USA.

GI Illness in Returned Traveler

GI illness is one of the most common illnesses in the returned traveler [13]. A history of destination, activities during travel, and onset of symptoms can help distinguish whether or not the illness is travel related. A more in-depth discussion of traveler's diarrhea is reviewed in the pre-trip consultation section of this chapter.

Diarrheal symptoms lasting more than 2 weeks should prompt screening for *Giardia,* amebiasis, and other parasites. Multiple stool samples for O and P testing may need to be submitted to accurately diagnose parasitic infection. Three stool O and P samples on 3 different days is preferred, as 1 sample can miss potential infection dependent on time of collection. In cases where clinical suspicion persists despite negative microscopic results, stool testing for *Giardia* and *Cryptosporidium* antigen is available and is sensitive.

Extended symptoms of diarrhea can also be seen with postinfectious irritable bowel syndrome (IBS), a diagnosis of exclusion in travelers with prolonged diarrheal symptoms more than 30 days after travel [29]. The incidence of postinfectious IBS is variable and ranges from 4% to 31% across all studies [29]. In one study of North American travelers to Mexico, the incidence was 11% of all travelers with diarrhea, with 10% of this number being newly diagnosed cases of IBS [30]. There is no widely accepted strategy for treatment, but options are similar to those recommended for noninfectious IBS including probiotics, antispasmodics, and low doses of tricyclic antidepressants [30].

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A subset of patients who return from travel present with symptoms that they attribute to parasites, with no objective findings to support this belief. In many such patients this belief can become fixed and life-altering. Many will travel from specialist to specialist seeking help. While this phenomenon can be a manifestation of pre-existing psychiatric disorders, it can present in those who are otherwise normal. An approach to delusional parasitosis is to perform limited reasonable rule-out procedures, offer a rational inexpensive empiric treatment, seek to establish a therapeutic relationship, and encourage the patient to accept that like phantom pain, the body sometimes tells the patient that there is a parasite when the parasite never was there, or was successfully treated, and these feelings can be helped by atypical antipsychotics.

Skin Lesions in the Returned Traveler

Skin lesions and rashes are common after return from travel. They may reflect a discrete condition (i.e., cutaneous larva migrans, swimmers itch, or tungiasis) or a systemic illness (i.e., dengue, chikungunya). History of activities during travel and specific locations visited during travel are important in the diagnoses of these conditions.

Eosinophilia

Perhaps the most common laboratory abnormality in a returned traveler is eosinophilia. Rather than focusing on the percentage, and absolute eosinophilia of 500×10^6 or higher should prompt further evaluation. The most common causes of eosinophilia in travelers are schistosomiasis, filariasis, and nematode infections [31], but *Strongyloides stercoralis* is an important consideration and may present decades after a stay in the tropics. Stool for ova and parasites may shed light on certain species of schistosomes and nematodes. Urinalysis should be performed for hematuria and schistosomal ova. Skin exam and a snip test can be helpful with filariasis.

Tuberculosis Screening in the Returned Traveler

In travelers to some destinations, especially developing countries, screening for tuberculosis on return is advised. If the trip itinerary includes a work in healthcare settings or frequent face-to-face contact with persons residing in a TB-endemic location, a PPD screen is recommended 8 weeks after return [32]. In some populations, a PPD may not be appropriate. These would include travelers with a history of BCG vaccine, as immunity is variable and a PPD test in these populations may be positive for decades. For these special populations, an interferon gamma release assay (IGRA)-based test such as QuantiFERON®-TB Gold is preferable for screening [33]. In populations in which there are no special indications for IGRA-based testing, there is no superiority of the IGRA-based test over the PPD test for screening [33]. For travelers who convert either their PPD- or IGRA-based screening to positive, a chest x-ray is recommended to assess for active tuberculosis. Persons with active disease are reportable to the local health department. Persons with latent disease should receive a discussion on the risks and benefits of treatment for latent tuberculosis. The McGill University decision tool is a very useful guide for such discussions [34].

Reentry for Long-Term Travelers: Psychological Concerns

For many return travelers who have been abroad long-term, reentry into life in the United States can be difficult. A variety of emotions can arise on the return, from happiness to anger and sadness. Long-term expatriates can feel isolated and unable to connect with loved ones from home after their experiences abroad. Reverse culture shock can occur as well. Screening for depression, anxiety, and PTSD should be considered for all long-term returned travelers when seen by their primary care providers, especially for those who may have suffered adverse events, or who were required to

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return involuntarily. Counseling is highly recommended for travelers with psychological concerns on reentry.

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Part III

Pregnancy, Childbirth, and Postpartum Care

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Preconception Care

9

Stephen D. Ratcliffe, Stephanie E. Rosener, and Daniel J. Frayne

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Preconception and Interconception Care Defined

Preconception care is defined as *a set of interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management* [1]. Interconception care is care provided to women beginning with childbirth until the birth of a subsequent child. It is a subset of preconception care that addresses the continuity of risk from one pregnancy to the next [2]. Preconception and interconception care has increasingly been recognized as a crucial component of both women's and infant's health.

Ongoing Problem of Perinatal Morbidity and Mortality

Infant mortality remains a significant problem in the USA. In 2017, the US infant mortality rate was 5.8 per 1000 live births. Despite leading the world in healthcare expenditures, the USA ranks 34th among developed nations in infant mortality [3]. Since 2000, after 40 years of improvement, infant mortality rates continue to be unacceptably high, and maternal morbidity and mortality are *increasing* [4, 5].

The most important causes linked to infant mortality are preterm birth and birth defects (Fig. 1). Birth defects account for 20.4% of all infant deaths and affect 1 in 33 infants born in the USA. Approximately 36.3% of all infant deaths in the USA are attributable to prematurity [6]. After decades of focus on improving prenatal care interventions, the preterm birth rate in the USA remains unacceptably high. Significant racial and ethnic disparities persist. For example, the perinatal infant mortality rate among non-Hispanic black infants is 2.3 times higher than that of white infants [7].

Even more striking is the stark contrast in the maternal mortality rate in the USA compared to other countries in other first world countries (Fig. 2). There is a 350% increase in maternal mortality rates among African American women compared to Anglo and Hispanic women resulting in the development of a number of contemporary initiatives to address these critical public health, access to care, and institutional racism issues [8, 9].

Need to Address Risks Prior to Pregnancy

It is now recognized that many of the modifiable risk factors affecting preterm birth, birth defects, maternal morbidity, and both maternal and infant mortality occur prior to pregnancy. Structural organogenesis of the central nervous system and

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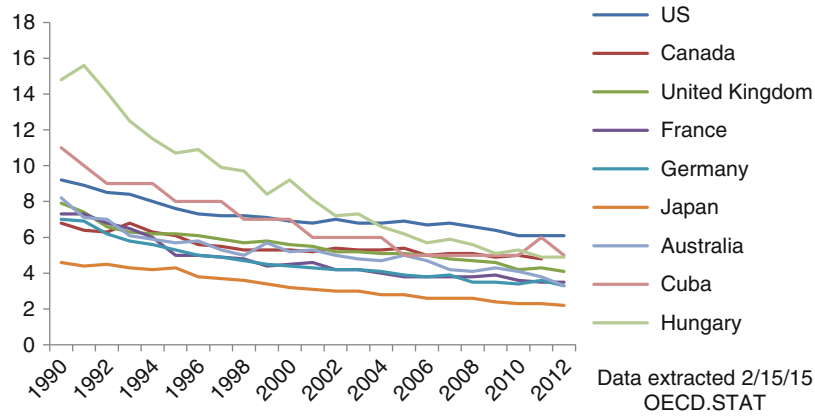


Fig. 1 1990–2017 country comparison infant mortality (per 1000 live births). (Data extracted 4/19/20 OECD. STAT)

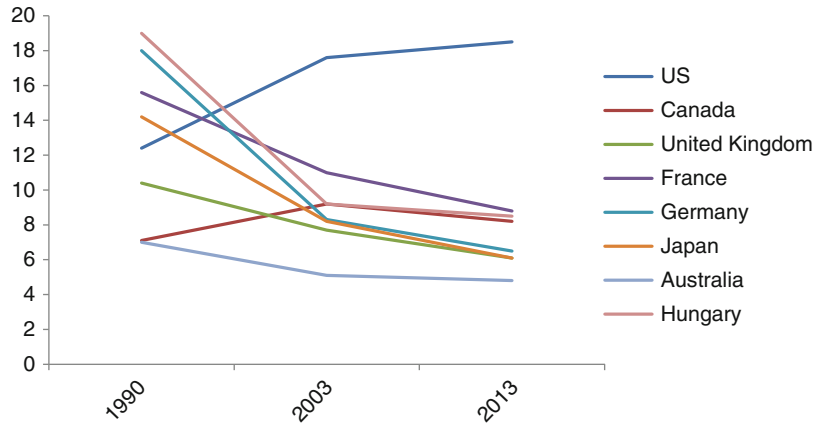


Fig. 2 1990–2017 country comparison maternal mortality (per 100,000 live births). ([5], WHO, UNICEF, UNFPA, World Bank Group, and the United Nations Population Division. Trends in Maternal Mortality: 2000 to 2017. Geneva, World Health Organization, 2019 (Accessed 4/19/20))

heart begins as early as 3 weeks' postconception, and the development of the heart, limbs, and reproductive organs is nearly completed by 8–9 weeks' gestation. As early as the missed menses and by the time a woman enters prenatal care, it is often too late to affect periconception risks [10]. Unfortunately, almost half of all pregnancies in the USA are unintended, thus limiting the ability to "plan" preconception risk reduction [11]. Unintended pregnancy is a risk factor for poor birth outcomes likely through uncontrolled health conditions or maternal behaviors. Additional examples of maternal risk factors that determine birth outcomes are interpregnancy interval, maternal age, exposure to teratogenic medications, exposure to substances, chronic disease control, and preventable congenital anomalies [12] (Table 1).

CDC Recommendations on Preconception Health

In 2006, the CDC released "Recommendations to Improve Preconception Health and Healthcare – United States: A Report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care" [1]. This report included ten recommendations to improve women's health and address the problem of preterm birth, birth defects, and infant mortality through increased focus on preconception care. Recommendation #3: "As a part of primary care visits, provide risk assessment and educational and health promotion counseling to all women of childbearing age to reduce reproductive risks and improve pregnancy outcomes." The select

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Table 1 Estimated prevalence of selected preconception health measures reported by the behavioral risk factor surveillance system and the pregnancy risk assessment monitoring system, USA, 2009 [12]

		Age group (years)				Race/ethnicity[a]			
Preconception measure		Total	18–24	25–34	35–44	White	Black	Others	Hispanic
Healthcare	Insurance coverage[b]	74.9	62	79.8	84.6	81.9	76	82.9	50.3
	Preconception counseling[c]	18.4	18.3	19	16.4	17.6	21	16.2	20.6
	Postpartum visit[d]	88.2	83.7	90.5	90	91.6	86.6	88.3	80.3
Reproductive health and family plan	Prior preterm birth[e]	14.4	16.8	14.1	12.1	12.6	17.5	13.5	17.1
	Recent fetal loss[f]	14.9	12.8	13.6	21.9	14.6	15.7	21.8	13
	Unintended pregnancy[e]	42.9	61.6	35.4	29.2	37.3	65.2	37.9	45.9
	Unintended pregnancies not on contraception[e]	52.6	54.5	51.1	51.3	54.1	54.5	55.4	45.9
	Postpartum contraceptio[e]	85.1	86.2	85.2	82.4	85.9	83.7	78.7	85.7
Tobacco and alcohol use	Current tobacco use[b]	18.7	18.7	20.4	17.2	22	15.7	16.9	9.8
	Prepregnancy tobacco use[e]	25.1	35.8	21.7	14.1	30.8	22.7	18.7	12.4
	Recent binge drinking[b]	15.2	21.2	15.8	11.7	17.9	10.1	11.7	11
Nutrition and physical activity	Overweight (BMI 25.0–29.9)[b]	26.6	21.6	27.7	28.3	25	28.4	25.6	31.1
	Obesity (BMI $\geq$30)[b]	24.7	16.6	25.8	28	21.7	39.6	18.2	28.2
	Multivitamin use[e]	29.7	16.1	34.5	42.4	34.2	19.5	33	22.5
	Adequate physical activity[b]	51.6	53.5	52.8	49.7	55.3	41	46.8	47.7
Mental health	Frequent mental distress[b]	13.2	12.9	13.8	12.9	12.8	15.1	12.9	13.4
	Anxiety or depression[e]	11.2	12.1	10.9	10.4	13.2	9.8	7.9	7.3
	Postpartum depression[e]	11.9	14.7	10.7	10	11.8	14.1	10.2	11.1
Emotional and social support	Recent physical abuse[e]	3.8	6.7	2.6	1.9	3	5.7	3.1	5
	Adequate social/ emotional support[b]	79.9	80.3	80	79.6	85	69.7	74.9	70.5
	Adequate social support postpartum[f]	87	86.6	86.9	89.4	90.6	79.4	87.2	75.5
Chronic conditions	Diabetes[b]	3	1	2.4	4.5	2.3	5.1	3.3	3.6
	Hypertension[b]	10.2	4.7	8.5	14.7	9.3	19.2	7.9	8.2
	Asthma[b]	10.7	12.9	10.2	9.8	11.3	12.3	9.8	7.7

[a]White, non-Hispanic white; Black, non-Hispanic black; others, non-Hispanic others
[b]BRFSS, USA
[c]PRAMS, 4 reporting
[d]PRAMS, 16 reporting
[e]PRAMS, 29 reporting
[f]PRAMS, 2 reporting
(MMWR/April 25, 2014/Bol. 63/No. 3)

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panel also recommended to (1) encourage each woman and couple to have a reproductive life plan; (2) deliver preconception interventions as follow up to risk screening, focusing on those interventions with high population impact and sufficient evidence of effectiveness; and (3) use the interconception period to provide intensive interventions to women who have had a prior adverse pregnancy outcome (e.g., infant death, low birth weight, preterm birth).

As part of its goal to reduce infant mortality and decrease disparities in reproductive outcomes, the CDC incorporated preconception care into *Healthy People 2020* and launched the Preconception Health and Healthcare (PCHHC) initiative focusing on five areas of engagement: clinical, consumer, public health, policy/finance, and surveillance/research [12]. In 2008, the clinical working group of the PCHHC published a systematic review of the evidence in support of the clinical content of preconception care. More than 30 experts reviewed over 80 topics using the strength of recommendation taxonomy approach consistent with USPSTF. This compendium of evidence has informed the distillation of preconception care into ten focused content areas of risk reduction and intervention to improve future birth outcomes: family planning, nutrition, infectious disease/immunizations, chronic disease management, medication and environmental exposures, substance use, previous pregnancy outcomes, genetic history, mental health, and interpersonal violence [13].

Barriers

Unfortunately, there remain significant barriers to successful implementation of quality preconception health. Women often do not seek reproductive healthcare prior to pregnancy, and a large proportion of women of reproductive age do not have insurance coverage until they are already pregnant [14]. When there is an opportunity in a clinical setting, there is often insufficient time to address preconception health [15]. Other health issues often take priority, and preconception care is usually not the reason for visit. When it comes to interconception care, the focus is more often on the child than on the woman's health [16, 17]. Finally, providers may lack education, guidance, or resources on approaching preconception health issues in the continuum of care [15].

Opportunities in Primary Care

Despite evidence that managing preconception health can help to improve pregnancy outcomes, many women do not receive this care [18]. Nationally, of women aged 18–44, only 46.5% received appropriate contraceptive counseling, 45.3% with risk for infection were tested for chlamydia, 33.2% had preconception counseling. While 80.9% had their blood pressure checked, only 44.9% with obesity were counseled about ways to improve diet, and 55.2% of smokers received counseling to quit [19]. Family physicians and other primary care providers have many opportunities to interact with women of childbearing age and provide this care during well-woman exams, acute care, and chronic disease management visits, as well as when they accompany their children or partners to their visits. "It is not a question of whether you provide preconception care. Rather, it's a question of what kind of preconception care you are providing" (Stanford and Hobbins) [20]. Making preconception health a part of routine primary care could significantly impact the health of women and future pregnancies as well as the health of infants and children.

History

Past Medical History

A thorough past medical history is the cornerstone of comprehensive primary care and equally so in the provision of preconception care. More than 25% of women of childbearing age have a chronic condition such as chronic hypertension, asthma, major depression, etc. (Table 2). It is essential that these chronic conditions be recognized and treated in the preconception period [23, 24]. For example, poorly controlled or undiagnosed diabetes resulting in hyperglycemia in the first

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Table 2 Preconception Care of Common Medical Conditions

Condition	Epidemiology/natural history	Preconception interventions	Contraception strategies	Medication use
Diabetes mellitus (DM) and relationship to gestational diabetes (GDM)	One percent of pregnancies with DM and 7% with GDM. Poorly controlled DM in the first trimester associated with fourfold increase in congenital abnormalities. High rate of recurrence of GDM. Fifty percent GDM develop DM within 5 years	Strict glycemic control of DM in the first trimester reduces the risk of congenital malformation. Lifestyle modification decreases risk of developing DM among women with previous history of GDM	Avoid use of estrogen-containing birth control if patient with DM has concurrent hypertension, renal disease, or thrombophilia	Diabetic medications such as sulfonylureas, metformin, and insulin safe to use in pregnancy
Thyroid conditions	Graves (0.2% prevalence) untreated: poor outcomes Overt hypothyroid (2.5%) Untreated: decreased IQ and increased spontaneous AB and preterm delivery Subclinical hypothyroidism (2–5%) associated with adverse perinatal outcomes	Hypothyroid: levothyroxine should be increased 25% as soon as pregnancy diagnosed Subclinical hypothyroid: RCT evidence for screening and treatment lacking	Overt hypothyroidism and subclinical hypothyroidism are associated with impaired fertility and increased risk of miscarriage	Graves: avoid methimazole in the first trimester; avoid use of propylthiouracil in the second and third trimester Hypothyroid: maintain TSH below 2.5 in the first trimester
Epilepsy	One percent of population; 3–5/1000 births; increased congenital anomalies in women who have seizures and who take antiseizure meds (two to threefold increase)	Discontinue antiseizure meds if seizure-free for 2 years; switch to meds that are less teratogenic before pregnancy such as lamotrigine and levetiracetam	Decreased efficacy of OCs when taking meds that induce liver enzymes, i.e., phenytoin and carbamazepine; use progesterone-only contraceptive methods if using these medications	Consider switching to safest alternative medication – experts do not suggest immediate cessation of therapy due to possible increased risk of seizures; use high-dose folic acid (4 mg/day) 4 weeks before and 12 weeks after conception
Chronic kidney disease (CKD)	Patients with mild CKD (creat 0.9–1.4) have good outcomes. Patients with moderate CKD (1.4–2.5) or severe (>2.5) at risk of developing worsening disease. These patients have increased risk of adverse outcomes if they have HTN	Very important to control blood pressure. Try to avoid pregnancy with moderate to severe CKD	Absolute contraindication to use estrogen OCs with CKD if they have cardiovascular disease and history of VTE and are smokers >35 and patients with liver disease. Use progesterone-only or barrier methods	Avoid use of ACEs, ARBs, and spironolactone in pregnancy

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Table 2 (continued)

Condition	Epidemiology/natural history	Preconception interventions	Contraception strategies	Medication use
Cardiovascular disease (CVD)	Three percent of women have CVD with a 1% incidence in pregnancy. CVD is the cause of 10–25% of maternal mortality. Conditions that result in NYHA class greater than II or cyanosis at baseline prenatal visit are most predictive of increased risk of perinatal and maternal mortality	Use of warfarin in pregnancy should be avoided; instead, heparin or enoxaparin is used. With prosthetic valves, warfarin may be used in the second and third trimester. Structural heart lesions should be repaired prior to pregnancy. Certain cardiac syndromes have genetic etiology	Important to have thorough cardiac assessment/imaging prior to pregnancy to assist in risk stratification of patients at high risk of morbidity and mortality Avoid COCs for patients with R to L shunts and ischemic disease and for patients with multiple cardiac risk factors. Progestin use is okay	Do not use warfarin in the first trimester. Avoid use of ACE, ARBs, and spironolactone in pregnancy
Hypertension (HTN)	Ten percent of women of childbearing age; women with chronic HTN at increased risk of worsening CKD, preeclampsia, and eclampsia in pregnancy	Preconception treatment of mild-to-moderate HTN results in 250 women needing treatment to prevent one fatal or nonfatal cardiovascular event such as a stroke	Combination OCs may be used in women with mild essential hypertension (140–159/90–99); copper IUD listed as preferred contraception for moderate to severe HTN	ACEs and ARBs are teratogenic and fetotoxic; should be stopped prior to conception
Asthma	Eight percent of pregnant women; 30% of women with asthma have worsening symptoms in pregnancy. Increased maternal and perinatal morbidity and mortality among women with poor control of asthma	Use of systemic steroids in the first trimester associated with threefold increased risk of oral clefts and maternal preeclampsia	Anticholinergic agents are class B and short-acting beta agonists are class C. Budesonide is class B and other inhaled corticosteroids are class C. Maternal smoking cessation is of great importance	Avoid use of systemic steroids in the first trimester. Administer influenza vaccine early in pregnancy
Thrombophilia	Factor V Leiden gene present in 5% of Caucasians; antiphospholipid antibody syndrome most common acquired condition and is more common in blacks Thrombophilias are associated with increased risk of VTE, arterial thrombosis, and severe preeclampsia	Diagnostic testing available for high-risk populations: FH of VTE, personal Hx of VTE; Hx of recurrent pregnancy loss, severe preeclampsia, severe IUGR Consensus expert opinion recommends treatment for many of these conditions in pregnancy; recommend MFM consultation	Genetic counseling and targeted screening indicated for high-risk populations during preconception care Combined OCs not recommended; progestin-only methods, IUDs, and barrier methods preferred	Use heparin or enoxaparin throughout pregnancy. Avoid use of warfarin, especially in the first trimester

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Table 2 (continued)

Condition	Epidemiology/natural history	Preconception interventions	Contraception strategies	Medication use
Obesity	More than one third of US women are obese which is associated with increased risk of DM, HTN, CVD, OSA, and cancers (breast, uterine, colon) Associated adverse perinatal outcomes include NTD, GDM, HTN, PTD, VTE, IUFD	Important to achieve weight loss prior to conception. Counseling alone or combined with medication can result in modest and sustained weight loss (USPSTF). Bariatric surgery prior to pregnancy is another effective intervention. This surgery is associated with increased fertility rates [21]	Clinicians need to assess obese women for comorbid conditions such as DM, HTN, and OSA and hx of VTE that markedly increase risk to women. With many of these conditions, use of combined OCs is relatively contraindicated. Increased risk of impaired fertility and early pregnancy loss	Bariatric surgery associated with decrease incidence of DM, GDM, HTN, and OSA but increased risk of preterm delivery, SGA, and NICU admissions. Increased risk of nutritional deficiencies with GI bypass surgery, less so with gastric banding [22]
Major depression/ bipolar	Approximately 12% of women in both the preconception and interconception periods have major depression [11]. Victims of intimate partner abuse have a fivefold increase in major depression. Major depression in pregnancy associated with increase in PTD and low birth weight. Bipolar disease associated with increased incidence of postpartum psychosis	Optimizing depression care with medication and psychotherapy associated with improved pregnancy outcomes [20]	Victims of intimate partner abuse have higher incidence of unplanned pregnancy and high-risk sexual behavior. Consider use of long-acting reversible contraception (LARC) for patients who find it difficult to use other daily methods	Patients receiving valproic acid and carbamazepine should be placed on 4 mg of folic acid/day for 4 months prior to conception. Valproic acid should not be used in pregnancy. Avoid use of paroxetine and lithium in the first trimester. Lithium can be used in the second/third trimester

trimester results in a fourfold increase in congenital heart defects and increased risk of pregnancy loss [25].

Previous Obstetrical History

Women who have had three or more spontaneous abortions should undergo additional testing to rule out thrombophilia, thyroid dysfunction, uterine anomalies, and other potential genetic syndromes. Women with a history of a spontaneous preterm delivery are at increased risk of this outcome in the next pregnancy [26]. Women with a prior history of preeclampsia, gestational diabetes, or other poor birth outcomes should have additional evaluation for chronic medical conditions such as diabetes mellitus and essential hypertension and undergo counseling on the importance of preconception and early prenatal care.

Family History

A three-generation family history can identify women who are at increased risk for genetic syndromes such as thrombophilia, coagulopathies, hemoglobinopathies, cystic fibrosis, trisomies, etc. In addition, it is important to obtain ethnicity information about both sides of the family.

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Genetic counselors may be of assistance for patients with positive three-generation family history screening. The carrier frequency for some of these conditions is also increased in selected ethnicities such as African, European, Ashkenazi Jewish, Mediterranean, and Asian descent [27].

Patients identified at increased risk of having a baby affected by one of these syndromes by virtue of a strongly positive family history or belonging to an ethnic group with a higher incidence of these conditions can undergo preconception expanded carrier screening. When one partner is identified to be a carrier, her partner can then undergo this same carrier screening [28].

"Cascade testing" of close relatives is often utilized to identify other family members affected by these conditions [29]. The following site provides summaries of up-to-date genetic conditions and testing recommendations: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/Medical-Genetics-Practice-Resources.aspx.

Social History

Poverty and the constant stressors associated with housing and food insecurity are the norm in many clinical settings. It is important that women living in poverty are given clear instruction and logistical assistance to access available social service resources. These resources vary from community to community, and the clinical team should be actively involved in linking patients to these resources.

Women who are currently experiencing or have a history of intimate partner violence are at marked increase of physical and emotional injury. A national survey in the late 1990s estimated that approximately 4.8 million partner rapes and physical assaults occur in the USA on an annual basis [30]. It is important to screen for exposure to violence routinely in the office setting. The CDC has extensive resources at https://www.cdc.gov/violenceprevention/pdf/ipv/ipvandsvscreening.pdf.

Smoking exerts deleterious effects on the current and future health of women and future pregnancies. Although smoking rates have been declining in the USA since 1990, an estimated 18.7% of non-pregnancy reproductive-aged women were smoking in 2009 [31].

Women using illicit drugs have a higher incidence of medical, psychiatric, psychosocial, and infectious comorbidities. Illicit drug use/abuse is common in rural and urban settings, often putting women at increased risk of significant morbidity and mortality. Ten percent of women of reproductive age report illicit drug use in the past month [12].

Approximately 54% of non-pregnant women of childbearing age consume alcohol and approximately 15.2% binge drink [12]. Women with alcoholism are at marked increased risk for adverse future pregnancy outcomes because alcohol is both a teratogen and fetal toxic agent. There is no known safe level of alcohol ingestion in pregnancy.

Medication History

It is important to review all prescribed and over-the-counter medications and to note which ones could exert teratogenic effects on the developing embryo. About 10–15% of congenital birth defects are thought to be caused by teratogenic exposure. Many anticonvulsant agents, most notably valproic acid and carbamazepine, markedly increase the incidence of neural tube defects. A valuable source for identifying prescriptive and OTC medications that pose risks to the developing embryo can be found at https://mothertobaby.org/fact-sheets-parent/.

Environmental History

Women should be assessed for exposure to major environmental agents including mercury, lead, hydrocarbons, bisphenols (organic compounds with estrogenic properties), and nitrates. These exposures may come from the workplace, hobbies, exposure from well water, contact from plastic containers (#7 plastic containers), or dietary sources (ingestion of large game fish). Clinicians and patients both need to be conversant about these common exposures in the environment [32].

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Physical Examination

The physical exam, in combination with a thorough history, offers the best opportunity to diagnose chronic medical conditions that can adversely impact a woman's current or future health.

Nutritional Status

When conducting the preconception physical examination, the clinician should determine the patient's BMI. Underweight women will have a BMI less than 19.8, while obese women will have a BMI greater than 30. Both of these extremes should trigger more extensive nutritional assessments/screening for eating disorders. Obese women have increased risk of developing hypertension, diabetes, cardiovascular disease, infertility, sleep apnea, and breast/uterine/colon cancer. Health risks of women with low BMIs include nutrient deficiencies, cardiac arrhythmias, osteoporosis, amenorrhea, and infertility [33].

It is important to ask patients about their use of dietary and nutritional supplements. Between 18% and 52% of women of childbearing age consume some kind of OTC dietary supplements. Excessive amounts of the fat-soluble vitamin A (>10,000 IU/day) may be teratogenic and can result in cranial and neural crest defects [21].

The Obesity Epidemic

One third of women are obese. Obesity is associated with an increased risk of type 2 diabetes, hypertension, cardiovascular disease, and other comorbid conditions. Maternal cardiovascular disease is the greatest contributor to maternal mortality. Behavioral, medical, and physical activity therapies aimed at losing 5–10% of total body weight over a 6-month period prior to pregnancy are thought to be realistic.

The provision of long-acting reversible contraception (LARC) to obese women is both safe and effective. The use of emergency contraception and the use of the contraceptive patch are less effective. The use of combined oral contraceptives for obese women is associated with a five- to tenfold increase in venous thromboembolism [22].

Bariatric surgery often leads to greater weight loss. A meta-analysis of 33 studies with 14,880 pregnancies that occurred after bariatric surgery and close to 4 million controls showed an increase for perinatal mortality (OR = 1.38, CI 1/03–1.85), congenital anomalies (1.29, CI 1.04–1.59), preterm birth (OR 1.57, CI 1.38–1.79), and NICU admission (OR 1.41, CI 1.25–1.59). These data suggest the need for specific preconception and prenatal nutritional support and increased fetal surveillance during pregnancies that follow bariatric surgery [34].

Standard Nutritional Recommendations

Women should be counseled on the importance of consuming a healthy, well-balanced diet that is high in fruits and vegetables with a low amount of refined carbohydrates and processed food. Women without a history of a previous pregnancy complicated by a neural tube defect (NTD) should be placed on a multivitamin supplement containing at least 400 mcg of folic acid. This is not only effective in preventing 70% of future neural tube defects but also results in a decreased incidence of limb, cranial facial, and urologic congenital birth defects [35]. Women with a previous history of an infant with a NTD require a much higher amount of daily supplementation with folic acid of 4000 mcg [36].

Vaccine Preventable Infections

Women of reproductive age should be counseled about vaccine preventable infections and offered appropriate immunizations according to the CDC ACIP recommendations [37, 38]. Particularly important for preconception health are hepatitis B, rubella, varicella, annual influenza, and HPV (for those aged 11–26 years).

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Sexually Transmitted Infections (STIs)

It is important for the clinician to develop skills in taking a thorough and sensitive history that identifies a patient's gender identity, sexual orientation, sexual history, and practices. The USPSTF has established screening and counseling recommendations for the following STIs: chlamydia, gonorrhea, hepatitis B, hepatitis C, herpes simplex, syphilis, and HIV. For patients at increased risk of contracting HIV, the use of once-daily treatment with tenofovir/emtricitabine (Truvada) is FDA approved for pre-exposure prophylaxis and is recommended by the USPSTF [39].

Laboratory Evaluation

Women should be screened for diabetes according to current USPSTF guidelines. Screen for anemia for patients with a history of excessive menstrual blood loss, those whose physical exam is suggestive of anemia, or whose family history is positive for hemoglobinopathy.

Strategies for the Prevention of Adverse Birth Outcomes

The traditional approach of addressing maternal risk factors through a single preconception visit has failed to improve birth outcomes. Current recommendations focus on integrating preconception screening, risk reduction, and health promotion into all routine healthcare encounters for women with childbearing potential, regardless of pregnancy intention. Visits for preventive and routine gynecologic care provide natural opportunities for risk reduction, health promotion, and family planning. However, encounters for pregnancy testing, treatment of sexually transmitted infections, and management of chronic medical conditions provide unique opportunities for the delivery of preconception care and counseling. In each setting, advice should be tailored to the needs of patient based on individual attitudes, beliefs, preferences, and stage in the reproductive life span [1].

The Reproductive Life Plan

A key strategy for preconception health promotion is the development a reproductive life plan. Family physicians should encourage all men and women to explore their intention to conceive in the short and long term, taking into consideration their personal values and life goals. Once developed, patients should be educated about how their reproductive life plan impacts their contraceptive and medical decision-making. Because planned pregnancies are associated with improved outcomes for mothers and infants, women should be encouraged to make intentional decisions regarding the number and timing of pregnancies. The CDC has developed resources to assist healthcare providers and patients with developing a reproductive life plan which can be accessed at https://www.cdc.gov/preconception/planning.html.

Reducing Disparities

Family physicians should be aware that women of color are at increased risk for adverse pregnancy outcomes for both mother and baby. The cause appears to be multifactorial, and sociodemographic factors alone do not fully explain racial disparities in birth outcomes [40]. However, a large analysis of 2016 US birth certificate data revealed that the known portion of the disparity in preterm births between non-Hispanic black and white women was driven by sociodemographic and preconception/prenatal health factors [41]. This suggests that preconception interventions targeting these risk factors could potentially reduce racial disparities and improve perinatal outcomes. Other factors likely to contribute to disparities include unequal access to reproductive health services and a lack of comfort among women of color interfacing with the healthcare system. The Black Mamas Matter Alliance (https://blackmamasmatter.org), The National Latina Alliance for Reproductive Health (https://www.latinainstitute.org) and other organizations within the reproductive justice movement advocate at the national level to expand access to contraceptive services, prenatal and pregnancy

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care, and pregnancy termination services for women of color, work to eliminate systematic bias, and increase the voice of women of color within the healthcare system.

Novel Approaches to Preconception Care

In response to the lack of improvement in birth outcomes at the state and national level, many novel strategies for delivering preconception education, screening, and intervention have been developed including the following examples:

- *The Grady Memorial Hospital Interpregnancy Care Program (Atlanta, Georgia)* – In this groundbreaking program, low-income African American women with a history of very low-birth-weight delivery received individualized primary care services, intensive case management, and social support from multidisciplinary teams for 24 months following delivery. A significant reduction in rapid repeat pregnancies and adverse subsequent birth outcomes was achieved with an estimated net cost savings of $2397 per participant. The Grady program has been recognized as a successful model for improving birth outcomes by reducing disparities [42].
- *One Key Question*® (Power to Decide) – This initiative, originally developed by the Oregon Foundation for Reproductive Health, encourages all primary care providers to routinely ask women ages 18–50 "Would you like to become pregnant in the next year?" This question facilitates a conversation between providers and patients in which reproductive needs and preferences are explored [43]. Women are then offered essential preventive services based on identified needs (https://powertodecide.org/one-key-question).
- *The North Carolina Statewide Multivitamin Distribution Program* – This innovative program provided multivitamins with folic acid to low-income, non-pregnant women of childbearing potential to help prevent birth defects. Reported use doubled over a 10-month period among a sample of women receiving multivitamins through this program [44] (http://everywomannc.org/public-health/multivitamin-program/).
- *The IMPLICIT Network* – This collaborative of Eastern US family medicine and pediatric residency programs and community partners has implemented an evidence-based interconception screening and risk reduction intervention for mothers bringing their infants for well-child visits. Quality improvement techniques are used to improve care delivery, and future primary care physicians are trained in best practices (www.fmec.net/implicit.htm). The IMPLICIT ICC Toolkit is accessible at https://www.marchofdimes.org/professionals/implicit-interconception-care-toolkit.aspx.
- *Nurse-Family Partnership* – This program partners low-income, first-time mothers with a registered nurse early in pregnancy. Participating women receive ongoing nurse home visits through their child's second birthday. Nurses help mothers access good preventive and prenatal care, provide parenting support, and encourage self-sufficiency by helping mothers plan future pregnancies, continue their education, and find work (www.nursefamilypartnership.org).
- "*Show Your Love" Campaign* – This social marketing campaign launched by the CDC Preconception Health and Healthcare Initiative encourages women of childbearing age to maintain good health, reduce health risks, and make intentional decisions about pregnancy (https://showyourlovetoday.com).

Preconception Care and the Family

The health of a woman is interdependent with the health and well-being of her family. A woman's health is influenced by her family's medical history, culture, and view of health and illness. Some maternal risks for poor birth outcomes such as poor nutrition, smoking, and depression are associated with adverse effects

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for family members, especially children. The birth of a premature or critically ill newborn has a significant impact on family members. Parents experience stress related to uncertainty of the outcome, increased time away from work, financial burdens, and little time to spend with one another. Older children often experience anxiety due to separation from their parents, disruption of the family schedule, and a limited understanding of the newborn's condition. Family physicians should consider family values, beliefs, and influences (both positive and negative) when delivering preconception care emphasizing the goal of improving the health of all family members.

Preconception Issues for Men

Preconception care for men engages them in achieving planned, healthy pregnancies with their partners. Like women, men should be encouraged to develop a reproductive life plan to guide decisions about reproductive health. The CDC recommends that all men have a preventive care visit prior to conception to promote physiologic and emotional wellness, manage chronic health conditions, and educate men about the importance of avoiding sexually transmitted infections, substances, and toxic exposures. Men should be made aware of factors that can lead to decreased fertility and how to avoid them. Family physicians should also counsel men on the importance of supporting their partner in efforts to adopt a healthy lifestyle, follow treatment plans for chronic conditions, and take responsible steps to ensure planned, appropriately spaced pregnancies [45].

Key Preconception Care Partnerships and Resources

Family physicians should become familiar with the resources and partnerships in their community that provide preconception services for women. Examples include the local Health Department, Healthy Start Programs, Planned Parenthood, and WIC. State chapters of the March of Dimes also support programs that improve preconception health. Many national organizations have developed extensive preconception resources for clinicians:

- Center for Disease Control and Prevention, Preconception Health and Healthcare – Information for Health Professionals – summary of the content of preconception care for women and men, reproductive life planning tools, index of state and local resource, and collection of useful articles (https://www.cdc.gov/preconception).
- The National Preconception Curriculum and Resource Guide for Clinicians developed by the Preconception Health and Healthcare Initiative – includes the National Preconception/Interconception Care Clinical Toolkit, online continuing education modules, and a point of care mobile app (http://beforeandbeyond.org).
- National Healthy Start – HRSA-funded, locally administered programs that connect pregnant women and new mothers in at-risk communities with healthcare and support services through the child's first 2 years of life (www.nationalhealthystart.org).
- National March of Dimes, Resources for Professionals – includes prematurity prevention resources, genetic risk assessment tools, birth outcome statistics (PeriStats), and patient education resources (https://www.marchofdimes.org/professionals/professionals.aspx).
- Power to Decide (formerly The National Campaign to Prevent Teen and Unplanned Pregnancy) – information and resources for women, clinicians, and organizations with a goal of reducing unwanted pregnancy. Resources include the One Key Question™ clinician tool, Bedsider digital patient education resource, #Talking is Power Toolkit aiming to spark meaningful conversations between young people and trusted adults, a repository of contraception access data, and resources that support advocacy.

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Normal Pregnancy, Labor, and Delivery

10

Naureen B. Rafiq

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Pregnancy and childbirth are normal physiological processes for most women. Although an integral part of the fabric of pregnancy and birth is the availability of quality prenatal care to ensure the highest level of safety, modern medicine has sometimes been guilty of using a disease model for the management of pregnancy

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and childbirth, resulting in higher rates of complications.

The national US cesarean section rate was 4.5% in 1965 [1], when it was first measured, and steadily increased to the current rate of 32.8% in 2010/2011 [2]. More recent studies reaffirm earlier World Health Organization recommendations about optimal rates of cesarean section. The best outcomes for women and babies appear to occur with cesarean section rates of between 5% and 10%. Rates above 15% seem to do more harm than good [3].

In 1902, J.W. Ballantyne, a Scottish physician, introduced modern prenatal care. In the late nineteenth century, he observed that while much was done for mothers and babies during labor and birth, these activities did little or nothing to reduce the morbidity and mortality of congenital anomalies, multiple births, and fetal diseases. He identified maternal exposures including alcohol, nicotine, and lead and infectious diseases, such as syphilis and tuberculosis, as major fetal hazards and began promoting specific antenatal treatments to reduce their impact on pregnancy outcomes [4].

Beginning in 1907, Dr. Josephine Baker, noting Dr. Ballantyne's methods, began applying these principles to slum dwellers in New York City, among whom infant mortality rates were very high. Services were offered to pregnant women and extended to the postpartum period. Women were seen every 2 weeks in their homes by nurses until 7th month of gestation and then weekly until delivery. At these visits, nurses would inquire about danger signs, check blood pressure, urine, assess fetal heart tones, and provide advice about diet, hygiene, exercise, and preparation for the childs' arrival. This focus on good nutrition and screening for problems during pregnancy dramatically improved outcomes, bringing the maternal and infant morbidity and mortality rates to record lows.

Today, approximately 30% of family physicians provide maternity care. Women living in rural areas and smaller communities often have difficulty accessing maternity care because they reside in places that generally cannot support an obstetrician or a hospital with a labor and delivery suite. Instead they must travel to larger regional medical centers and may delay seeking prenatal care or are seen less frequently during their pregnancies. As a result, the need for family physicians to provide maternity care is particularly important in underserved and rural areas. Because the family physician is the physician for the father, mother, and the child makes them ideal to provide family-centered care.

Family-centered care means providing care in the context of the family. This practice considers, includes, and fosters the development of families with the birth of a child, as new relationships are made, family members taking new responsibilities for each other, the baby, and community. A family physician through family-centered maternity care not only respects the woman's autonomy but also helps guide her into shared decision making in accordance with her goals. This chapter reviews principles and practice of normal pregnancy, labor, and delivery.

Prenatal Care

Ideally, prenatal care starts well before conception. Planning for pregnancy helps to prevent complications and results in optimal maternal and fetal outcomes. Efforts should be made and opportunities utilized with women of childbearing age who present for health maintenance exams to counsel them on a healthy lifestyle, identifying social, behavioral, environmental, and biomedical risks that can affect fertility or pregnancy outcomes. Although many women will seek preconception counseling before attempting to become pregnant, in the USA about 50% pregnancies are unintended [5]. A reproductive health plan should be created and revised with each subsequent visit, taking into consideration contraceptive needs and the timing of pregnancy.

It is recommended that prenatal care should begin as soon as possible after conception, since organogenesis occurs at 3–10 weeks of gestation, but about 30% of women begin prenatal care in second trimester at or around 13 weeks.

Work, home, pets, hobbies, potential toxic exposures, nutrition, hygiene, chronic diseases, teratogenic medications, and substance abuse are

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some of the examples where early intervention can lead to better outcomes.

Traditional prenatal care involves monthly visits until 28 weeks of gestation, then biweekly until 36 weeks, and weekly until the delivery. This schedule may be modified based on risk factors and may be multidisciplinary as required [6].

The supplementation of folate for the prevention of neural tube defects (NTD) is an important intervention and may reduce the risk of NTDs three- to fourfold. Because at least 50% of pregnancies are unplanned, and organogenesis is usually well established before many women realize that they are pregnant, all women of childbearing age who are at average risk of bearing a child with an NTD should be counseled to take 0.4 mg of folate daily. Women at high risk should be counseled to take at least 4 mg of folate. Those at high or intermediate risk include those with a history of previous NTD, pregestational diabetes mellitus, those on anticonvulsants, having a BMI of >35 kg/m^2, and certain ethnic groups, such as Hispanics and Native Americans [7].

Vaccination of women with Tdap during pregnancy (ideally between 27 and 36 weeks gestation) helps to provide some protection to infants from pertussis until they are old enough to be vaccinated themselves. Tdap given to pregnant women stimulates the development of maternal antipertussis antibodies, which pass through the placenta, providing the newborn with protection against pertussis in early life, and will protect the mother from pertussis around the time of delivery, making her less likely to become infected and transmit pertussis to her infant [8].

First Trimester

The first trimester is from week 1 to the end of week 12. Amenorrhea is the cardinal sign of pregnancy in a woman of childbearing age with regular menstrual cycles and should prompt a pregnancy test to confirm this.

Patients may present with morning sickness that may strike any time of the day and can sometimes begin as soon as 3 weeks after conception. This is due to rapidly rising levels of estrogen and progesterone resulting in gastroparesis. Nausea has also been directly related to beta hCG levels and is considered one likely candidate for the emetogenic stimulus arising from the placenta. This nausea may be accompanied by heartburn for the same reason. Eating small frequent meals rather than three large meals and prescribing medications for intractable cases is helpful. It is imperative to ensure that patients have adequate urine output and do not become dehydrated.

Patients may have brief vaginal bleeding or spotting around the time of their usual menstrual cycle likely due to implantation of the embryo in the uterine wall. This may result in confusion on pregnancy dating.

Sore, tender, fuller breasts often occur and are caused by hormones preparing milk ducts to produce milk.

Constipation also occurs – also the result of progesterone causing reduced GI tract motility. Constipation may also occur as a result of iron in the prenatal vitamins. Regular physical activity, hydration, and increased fiber intake usually helps.

Fatigue is also very common during the first trimester and may go on into the second and third trimester. It is thought that progesterone may also have a role in helping to induce sleep. Increased rest and adequate intake of protein may be helpful.

Urinary frequency occurs due to the physical pressure of the urinary bladder on the enlarging uterus. Patients are advised to urinate frequently to help avoid incontinence and urinary tract infections.

Pregnancy causes dilation of blood vessels that tend to cause drops in blood pressure, which may result in postural dizziness and light-headedness. Patients are advised to avoid prolonged standing and to rise slowly after sitting or lying down.

Health Promotion/Counseling

Pregnant women are often more motivated to adapt healthy behaviors during pregnancy. A special effort should be made to counsel and educate women on healthy lifestyles during pregnancy, child birth, and parenting.

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Usually, the first prenatal visit is used for a comprehensive care plan but all prenatal visits should be considered potential counseling opportunities.

1. Patients should be counseled on number and frequency of visits.
2. Maternal weight, blood pressure, uterine growth, fetal activity, and heart rate are monitored.
3. Danger signs: Call the physician with danger signs such as vaginal bleeding, rupture of membranes, decreased fetal activity, and uterine contractions.
4. Seat belts and airbags: Patients should be advised to wear seat belts low across the lap and not to turn off airbags.
5. Nutrition and vitamins: Continue to take prenatal vitamins containing iron and folic acid. Suggestions to improve nausea and vomiting, constipation, and gastroesophageal reflux should be provided if present. Severe nausea and vomiting, ketonuria, and/or electrolyte abnormalities should be investigated to rule out other medical causes, and consider ultrasound to rule out twin or molar pregnancy.
6. Obesity: Obesity is common in pregnant women. They should be counseled on obesity-related complications and may benefit from early screening for gestational diabetes.
7. Gestational weight gain: For the majority of pregnancies, the average weight gain is 25–35 lb (11–16 kg), but a 10–14 lb (4–6 kg) weight gain in an obese female and a 40 lb (18 kg) weight gain in a lean female are also considered normal.
8. Alcohol, cigarettes, and substance abuse: Pregnant women should be strongly advised to quit smoking, alcohol, and any substance abuse to reduce their risk of low birth weight, mental retardation, preterm premature rupture of membranes, preterm labor, and other conditions.
9. Infection precautions: During influenza season, women should receive influenza vaccine regardless of trimester of pregnancy. Tetanus, diphtheria, and acellular pertussis should be administered to the mother in the third trimester of each pregnancy, preferably early in the third trimester.

   Advise mothers to avoid cat feces, such as cleaning out litter boxes, or eating raw or undercooked meat due to the risk of toxoplasmosis.

   If pregnant women are found to lack immunity to varicella or rubella, immunization should be administered immediately after delivery or termination of pregnancy.
10. Work: The effects of physical exertion that include long hours standing, exposure to heat, heavy metals, and hazardous gases should be evaluated and possibly modified on a case-by-case basis. Daycare and health–care workers should be cautioned regarding the risks of exposure to certain infections [9]. Most women should continue to engage in moderate physical activity, keep their heart rate below about 140/min and their body temperature within 1–2° of normal [10].

    Special attention should be paid to oral health. Preventive work or treatments should not be deferred.

    Saunas and hot tubs should be avoided, due to rapid changes in temperature.

    Sexual intercourse to be avoided in cases of undiagnosed vaginal bleeding or ruptured membranes.

Prenatal Screening

Prenatal screening is done for early detection of potential risks to the pregnancy. There are standard screening tests offered to all women, and more specific tests available for women with particular risks. The choice of tests should be evidence based and based also on the genetic history, ethnicity, psychosocial stress [11, 12], history of domestic abuse, and substance abuse.

Common Screening Tests in Pregnancy

First Trimester

Complete blood count

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Blood group and Rh factor
Antibody screen
Urine analysis and culture
RPR
Hepatitis B surface antigen
Rubella IgG
Varicella IgG
Papanicolaou smear
Gonorrhea and Chlamydia culture
"Opt out" HIV screening
Sickle cell screening in appropriate ethnic groups or suspicion
Hemoglobin electrophoresis considered in appropriate ethnic groups or suspicion
Counseling for Tay-Sachs and cystic fibrosis genetic testing
PPD if indicated

Second Trimester
Quadruple screen at 14–18 weeks in which levels of alpha-fetoprotein (AFP), estradiol, beta hCG, and inhibin are measured.
Amniocentesis if indicated
Ultrasonography for fetal age and anatomy

Third Trimester
1 h glucose test to screen for gestational diabetes
Repeat CBC
Repeat antibody screen if appropriate
Group B streptococcal screening at 35–37 weeks
Repeat GC/Chlamydia, RPR, and a check for bacterial vaginosis if indicated
Tdap at 28 weeks

Prenatal screening is discussed with each patient at the initial prenatal visit, and each prenatal test is evaluated to ensure that benefit outweighs the risks and complications.

Nuchal translucency with maternal serum screening markers is used to detect chromosomal abnormalities. Studies in the 1990s showed that decreased levels of pregnancy-associated plasma protein A and increased levels of free beta hCG combined with nuchal translucency (an echo free area at the back of fetal neck on ultrasound) have a comparable detection rate of Down's syndrome at 10–14 weeks to the second trimester quad screen [13–15].

Chorionic villous sampling (CVS) for chromosomal analysis is also offered at 10–14 weeks to all women 35 years or older. It has the advantage that it can detect Down's syndrome earlier than amniocentesis, but carries a slightly higher risk of miscarriage than amniocentesis.

Second Trimester

The second trimester is from the end of the 12th week to the end of the 27th week. There is usually significant improvement in nausea and fatigue.

The extra weight gained in the first 3 months often results in back pain. To ease the pressure, it is advised to practice good posture and use a chair that provides good back support. Sleeping on the side with a pillow tucked between the legs and avoiding excessive lifting may be helpful. It is advised to wear low-heeled, comfortable shoes with good arch support.

About half of pregnant women develop swollen, tender gums around this time. Hormonal changes send more blood to the gums, making them more sensitive and causing them to bleed more easily. Studies suggest that pregnant women with periodontal disease are prone to a number of adverse outcomes that include preterm labor and low birth weight [16].

Much of the breast tenderness experienced during the first trimester resolves. Often, a thin, milky white vaginal discharge (called leukorrhea) occurs in the second trimester of pregnancy. The use of tampons is discouraged. Vaginal discharge may increase. If the discharge is foul-smelling, green or yellow, bloody, or if there is a lot of clear discharge, investigations may be warranted.

Hemorrhoids are common in pregnancy due to increased blood flow and pressure from the gravid uterus.

By the midpoint of pregnancy around 20 weeks women start to feel the first delicate flutters of movement in the abdomen, known as "quickening."

Pregnant women often look as though they are "glowing" because changing hormone levels make the skin on the face appear flushed. An increase in the pigment melanin can also lead to

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brown marks on the face (chloasma, or the "mask of pregnancy") and a dark line (linea nigra) may be seen down the middle of the abdomen. Many of these skin changes typically resolve postpartum.

Thin, reddish-purple lines (striae) may appear on the abdomen, breasts, or thighs. These stretch marks emerge as the skin expands to accommodate the growing belly.

As morning sickness diminishes by the end of the first trimester the appetite returns. Caloric requirements increase by about 300–500 cal a day during the second trimester. Pregnant women should be gaining about 1/2 to 1 pound a week (226–453 g) at this time.

Health Promotion/Counseling

Most women who did not feel so great in the first trimester of pregnancy usually start to feel much better in the second. They gain weight more rapidly this trimester, adding as much as 4 pounds (1.8 kg) a month for the rest of the pregnancy.

Fetal growth, development, and movement accelerate in the second trimester with further development of most of the body organs. Women are advised to wear loose clothing to accommodate the growing belly. A childbirth class is a great way to prepare for labor and birth. Classes range from 1-day intensive workshops to weekly sessions lasting a month or more. The typical class consists of lectures, discussions, and exercises, all led by a trained childbirth instructor and usually covers the signs of labor, the normal progress of labor and birth, techniques for coping with pain, how a partner can help during labor, and when to call the doctor or midwife.

Patients are also counseled and encouraged to breast feed.

Second trimester bleeding should be evaluated carefully. It is not uncommon for women to experience self-limited vaginal bleeding after sexual intercourse. Rh negative patients should receive intramuscular RhoGAM at 28 weeks and after any bleeding or amniocentesis, if done.

Mothers are instructed to report any vaginal bleeding, new onset headaches, blurring of vision, significant edema, right upper quadrant pain, or changes in the frequency or intensity of fetal movement.

Second Trimester Screening

The quad screen – also known as the quadruple marker test is a prenatal test that measures the levels of four substances in a pregnant woman's blood: alpha-fetoprotein (AFP), a protein made by the fetus; human chorionic gonadotropin (HCG), a hormone made by the placenta; estriol, a hormone made by the placenta and the baby's liver; and inhibin A, another hormone made by the placenta. Typically, the quad screen is done between weeks 15 and 20 of pregnancy, in the second trimester, to detect chromosomal abnormalities and NTDs. Cell-free fetal nucleic acid testing in maternal blood is becoming available for various genetic conditions, as is noninvasive testing for fetal Rh in women who are Rh negative. Cell-free fetal DNA gets into the maternal bloodstream via shedding of placental microparticles. These can be detected as early as 7 weeks of gestation, and the level increases as the pregnancy progresses and quickly drops after the baby is born. Cell-free fetal DNA has been used to detect noncompatible RhD factors, X-linked genetic disorders, and single gene disorders. This test carries no risk of miscarriage, but has its limitations.

The results of these screens will help the mother make an informed decision whether or not to proceed to invasive testing for a number of genetic conditions. Amniocentesis is a confirmatory test that is able to sample whole chromosomes. It has slightly lower risk of complications than chorionic villous sampling.

Ultrasound dating is less accurate as the pregnancy progresses but uterus grows in a predictable manner in normal pregnancy. A 12-week uterus fills the pelvis and is a size of a cantaloupe. A 20-week uterus is the level of the umbilicus, and the fundal height usually corresponds in centimeters with the week of gestation measured from the pubic symphysis to the top of uterus. A fetal anatomical survey is done by a detailed ultrasound between 18 and 22 weeks of gestation for detection of physical anomalies.

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Third Trimester

The third trimester is from 28 weeks onwards. Biweekly visits until 36 weeks and weekly visits until delivery are recommended. The normal duration of pregnancy varies considerably but can be anywhere between 37 and 43 weeks. The fetus really fills out over these next few weeks, storing fat on the body, reaching about 15–17 in. long, and weighing about 4–4½ lb (1.8–2.0 kg) by the 32nd week. The lungs are not fully mature yet, but some rhythmic breathing movements occur. The bones are fully developed but are still soft and pliable. The fetus is storing its own calcium, iron, and phosphorus. The eyelids open after being closed since the end of the first trimester. Around 33–36 weeks, the fetus will descend into the head down position. The fetus is beginning to gain weight more rapidly. The lanugo hair will disappear from the skin, and it is becoming less red and wrinkled. The fetus is now 16–19 in. and weighs anywhere from 5¾ lb to 6¾ lb (2.6–3.0 kg).

At 38 weeks, the fetus is considered full term and will be ready to make its appearance at any time. Mom may notice a different quality of fetal movement, as the fetus is now filling the uterus with little room to move. The fingernails have grown long and small breast buds are present on both sexes. The mother is supplying the fetus with antibodies that will help protect against disease. All organs are developed, with the lungs maturing all the way until the day of delivery. The fetus is about 19–21 in. in length and weighs anywhere from 6¾ lb to 10 lb (3.0–4.5 kg).

RhoGAM may be given to Rh negative moms at 28 weeks if the antibody screen is negative.

Health Promotion/Counseling

The mother at this time is not just carrying an added 20–30 lb (or more) (9.0–13.6 kg), but the expanding uterus rearranges other organs in the body, adding even more strain. To avoid fatigue and increase energy it is often recommended to do small amounts of exercise. A walk, swimming, and prenatal yoga are good options. Taking short breaks at work, putting feet up, eating small, frequent meals and snacks also may help. Persistently low energy levels can be a sign of anemia and should be considered.

An expanding belly can throw off the posture, and the hormone relaxin, which loosens joints in anticipation of delivery, exacerbates the stress on the body.

Doing pelvic tilts, trying an under-the-belly support garment, supporting the back and abdomen with extra padding underneath the back, and keeping a wedge pillow between legs to create equilibrium for the hips can help. Nearly half of all moms-to-be will suffer from heartburn. Avoiding classic heartburn triggers is helpful. These include highly seasoned or acidic foods; greasy, fried, or fatty foods; and caffeine and carbonated drinks, citrus and some dairy foods, such as milk or ice cream. Switching from three meals daily to six easier-to-digest small ones, eating them sitting upright, and avoiding eating too close to bedtime or lying down right after eating also helps.

Over-the-counter remedies like Tums, Rolaids, Mylanta, Maalox, and Zantac are okay to take during pregnancy if lifestyle changes do not help.

The growing uterus puts pressure on the bladder most heavily in the third trimester leading to frequency of urination and sometimes urge incontinence. Trying to urinate on a schedule, such as every hour or two helps prevent this. It is also important to stay properly hydrated and to eat plenty of high-fiber foods to prevent constipation. Edema is caused by fluid retention in the lower half of the body. Varicose veins occur when valves inside blood vessels in the legs become soft or weak, which allows the blood to flow backward, pool, and form painful bulges. Although the swelling normally subsides, but sometimes varicose veins persist after pregnancy so to ease the discomfort of both edema and varicose veins, it is advised to elevate the feet often, switch standing and sitting positions frequently, not to cross legs, lie down whenever possible, preferably on the side, and to wear support hose, which may help soothe the aches and diminish the appearance of varicose veins. It is advised to avoid wearing anything that reduces circulation, like knee-high

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stockings and not to limit fluids to try to minimize puffiness. By 36–38 weeks patients may feel Braxton Hicks ("false") contractions. False contractions tend to be felt in the front of the abdomen only; whereas labor contractions tend to start in the back and come around to the front, sometimes moving from top to bottom of the uterus.

Third Trimester Screening

In women at average risk for gestational diabetes, a 50-g nonfasting 1-h glucose challenge test between 24 and 28 weeks of gestation is done. In contrast, women at high risk for gestational diabetes should be screened using the 50-g glucose challenge test at their first antepartum visit. Women who are at high risk for gestational diabetes include those with personal history of prediabetes, or diabetes in close family member, age more than 25 years, BMI of 30 or higher at the time of conception, history of gestational diabetes in previous pregnancy, and those of Black, Hispanic, American Indian, and Asian ethnicity. Screening cutoffs are 130 mg per dL (7.20 mmol per L; 90% sensitivity) or 140 mg per dL (7.75 mmol per L; 80% sensitivity). The most recent American Diabetes Association (ADA) and ACOG6 guidelines recommend either cutoff. Random or fasting glucose measurements are not recommended for screening because of poor specificity [17].

For women with a positive screening test, the 100-g 3-h oral glucose tolerance test is used to diagnose gestational diabetes. Although most organizations recommend a high-carbohydrate diet for up to 3 days before the test, a recent study showed that test results are not affected by modest variations in carbohydrate intake. Gestational diabetes is diagnosed if two or more plasma glucose measurements meet or exceed the following thresholds: fasting level of 95 mg per dL (5.25 mmol per L), 1-h level of 180 mg per dL (10.00 mmol per L), 2-h level of 155 mg per dL (8.60 mmol per L), or 3-h level of 140 mg per dL (7.8 mmol per L).

Vaginal and rectal swabs are taken at 35–37 weeks of pregnancy to detect group B streptococcus (GBS). GBS colonizes the vagina and gastrointestinal tract of up to 30% of all women and is the leading cause of early onset neonatal group B strep infection. Women who test positive are treated with intrapartum antibiotics to reduce the risk. The lower vagina, perineum, and rectum are cultured between 35 and 37 weeks of gestation and a positive culture is treated intrapartum with intrapartum penicillin G. In women with a high-risk penicillin allergy, clindamycin or erythromycin should only be used if susceptibility testing confirms the organisms' sensitivity. If it is not sensitive, or sensitivity results are not available, intrapartum vancomycin is recommended [18].

A complete blood count (CBC) is also recommended to check anemia at this time due to growing fetal needs.

Gonorrhea, chlamydia, RPR, and bacterial vaginosis are screened again in certain high-risk patient populations in the third trimester, although the cost versus benefit of treating for bacterial vaginosis is unclear. The United States Preventive Services Taskforce (USPSTF) recommends against screening for asymptomatic low-risk pregnant women and concluded with moderate certainty that screening has no net benefit. The results of assessing high-risk asymptomatic pregnant women were conflicting, and as a result the USPSTF concluded that evidence is insufficient to make a recommendation [19].

Fetal Assessment

The previously mentioned "kick counts" that mothers are instructed to perform and the general advice to report decreased fetal movement is the most widely applied method of fetal surveillance. Sensitizing the mother to the importance of detecting a change in fetal movement often provides the first indication of a problem with the pregnancy. Other early indications of a problem include a lack of weight gain and reduced growth velocity as reflected in small fundal height for dates. Assessment of the fetus remote from term is typically intensified as soon as a condition that increases the risk of fetal demise is recognized.

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Fetal heart rate monitoring: Electronic fetal heart monitoring (FHM) or intermittent auscultation is almost universally *performed as the first test* during pregnancy, labor, and delivery to identify the distressed and hypoxic fetus. The data to support improved outcomes with FHM are scarce and conflicting, but the long experience with this testing and the relative lack of availability of other methods to assess fetal condition in utero make FHM the most commonly utilized in the clinical setting.

Although there are many methods used to assess the fetus that include other options for noninvasive testing like Doppler velocimetry, umbilical artery Doppler flow assessment, and other ultrasound assessments, the most commonly utilized assessments include the nonstress test (NST), amniotic fluid volume, and the biophysical profile as well as the contraction stress test.

The NST is a simple low-risk procedure in which fetal heart rate is monitored along with simultaneous monitoring of uterine contractions through external monitors strapped around the abdomen. It is done every week after 32 weeks in many high-risk pregnancies. The fetal heart responds to uterine contractions with tachycardia. Two accelerations of 15 bpm lasting more than 20 s each within a 15 min period are reassuring and is considered reactive NST. This is recommended for women carrying more than one fetus, those with gestational diabetes, or gestational hypertension.

Contraction stress test (CST) is also carried out in high-risk pregnancies. A fetal monitor measures the baby's heart rate in response to contractions stimulated either by oxytocin (Pitocin) or nipple stimulation. Doctors use the measurements to predict how well the baby will cope with the stress of labor. They are also routinely applied for postdate pregnancies, intrauterine growth restriction (IUGR), oligohydramnios, polyhydramnios, decreased fetal movement, gestational diabetes and hypertension, Rh sensitization, or previous unexplained stillbirth. The contractions should occur within 30 min and last 40–60 s with a frequency of three in 10 min. A CST is positive if late decelerations are present with 50% or more of contractions. It is considered inconsistent if decelerations occur in fewer than 50%, and a negative CST has no decelerations.

A biophysical profile (BPP) combines the NST with an assessment of amniotic fluid index, fetal breathing movement, fetal activity, and fetal muscle tone. These parameters are assessed with ultrasound. It gives a reliable indication of fetal well-being. A score of 0–2 is given to each parameter.

A score of 8 or more is reassuring and indicates low risk for still birth. A score of 6 warrants further work up and is considered equivocal. Scores of 0–4 correlate well with a fetal pH of less than 7.2 and is an indication for immediate delivery.

Labor and Delivery

Three Stages of Labor

Labor is described in three stages, and together these stages complete the delivery of the fetus and passage of the placenta.

Stage One

The first stage is the process of reaching full cervical dilatation. This begins with the onset of uterine labor contractions, and it is the longest phase of labor. The first stage is divided into three phases: latent, active, and deceleration.

In the latent phase, the contractions become more frequent, stronger, and gain regularity, and most of the change of the cervix involves thinning, or effacement. The latent phase is most variable from woman to woman and from labor to labor. It may take a few days or be as short as a few hours. Typically, the latent phase lasts for 10–12 h for a woman who has had children. For first pregnancies, it may be closer to 20 h. For many women, the latent phase of labor can be confused with Braxton Hicks contractions. Membranes may spontaneously rupture in the early- to mid-portion of the first stage of labor. If they rupture, the labor process usually speeds up.

The next portion of the first stage of labor is the active phase, which is the phase of the most rapid cervical dilatation. For most women this is from 3 to 4 cm of dilatation until 8–9 cm of dilatation.

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The active phase is the most predictable, lasting an average of 5 h in first-time mothers and 2 h in mothers who have previously delivered.

Finally, there is the deceleration phase, during which the cervical dilation continues, but at a slower pace, until full dilation. In some women, the deceleration phase is not really noticeable, blending into the active phase. This is also a phase of more rapid descent, when the presenting part of the fetus is passing lower into the pelvis and deeper into the birth canal. The deceleration phase is also called transition, and, in mothers with no anesthesia, it is often punctuated by vomiting and uncontrollable shaking. These symptoms can be frightening to watch, but they are a part of normal birth, and they signal that the first stage is almost completed.

Stage Two

The second stage is the delivery of the infant. During the second stage, mom actively pushes out the baby. For first-time mothers, this can take 2–3 h, so it is important to counsel them to save energy and pace themselves. For second babies and beyond, the second stage often lasts less than an hour – and sometimes, only a few minutes.

Stage Three

The third stage of labor is the passage of the placenta, which can be immediate or take up to 30 min. The process may be sped up naturally by breastfeeding (which releases oxytocin) or medically by administering pitocin.

Support during Labor

Emotional and physical support significantly shortens labor and decreases the need for cesarean deliveries, forceps and vacuum extraction, oxytocin augmentation, and analgesia. Doula-supported mothers also rate childbirth as less difficult and painful than do women not supported by a doula. Labor support by fathers does not appear to produce similar obstetrical benefits. A number of studies report early or late psychosocial benefits of doula support. Early benefits include reductions in state anxiety scores, positive feelings about the birth experience, and increased rates of breastfeeding initiation. Later postpartum benefits include decreased symptoms of depression, improved self-esteem, exclusive breastfeeding, and increased sensitivity of the mother to her child's needs. A thorough reorganization of current birth practices is in order to ensure that every woman has access to continuous emotional and physical support during labor [20].

Intrapartum Analgesia

Maternal request is a sufficient medical indication for pain relief during labor. Laboring patients are educated about the different methods of analgesia that are available. Many pharmacological and nonpharmacological methods of labor analgesia have been adopted over the years. Nonpharmacological methods include support from labor attendants, doulas, changes of position, rest, ambulation, or a warm shower. Of the pharmacological methods, regional analgesia has become the most popular method. Short acting narcotics given in the first stage of labor are also commonly used, and may help facilitate dilation of cervix. Possible regional anesthesia techniques include epidural analgesia, spinal analgesia, or a combination of epidural and spinal analgesia. Approximately 60% of laboring women (2.4 million each year) choose regional analgesia for pain relief during labor [21].

Uterine contractions and cervical dilatation result in visceral pain whereas the descent of fetal head and subsequent pressure on the pelvic floor, vagina, and perineum generates somatic pain. Regional analgesia provides partial or complete loss of pain sensations below the T8 to T10 spinal level and is not just helpful in first and second stages of labor but also facilitates patient cooperation during labor and delivery, and if needed, procedures such as forceps or vacuum extraction.

It also allows extension of anesthesia for cesarean delivery if needed. Opioid-induced maternal and fetal respiratory depression can also be avoided. It also helps to control blood pressure in women with preeclampsia by alleviating labor

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pain, and it blunts the hemodynamic effects of uterine contractions and the associated pain response in patients with other medical complications. Possible adverse effects of epidural anesthesia are prolonged first and second stages of labor and the decreased maternal urge and ability to push. However, in spite of these drawbacks epidural anesthesia is extensively and routinely utilized in many hospitals and is requested by many women.

Delivery

Cervical effacement and dilatation is monitored every few hours. Anesthesia options should be reviewed with the patient early so that appropriate plans can be made.

Frequent spontaneous bladder voiding is encouraged. In patients with an epidural, a Foley catheter may be placed. Positioning options for the upcoming second stage of labor should be discussed. Mothers may ambulate and reposition themselves to maximize comfort. They may also eat small amounts of food throughout this stage, unless concern exists for impending difficulty during vaginal delivery and the possible need to convert to a cesarean section.

Delivery is imminent at crowning. Crowning occurs when the fetal head bulges the perineum as the head moves through the birth canal. A feeling of pressure due to distention of the perineum creates a tremendous urge to push for most women. Episiotomy should be avoided unless it appears that the perineum is obstructing progress or emergency delivery is required. If the mother does not instinctively feel when to push, as can occur with heavy anesthesia, she should be instructed to push with contractions.

Preparations for delivery are made when the fetal station is low. Drapes and gowns protect the clinician from the fluid of delivery; sterile preparation is not required. One hand is used to support and maintain the head in the flexed position as it delivers. The other hand is used to support the perineum. This will help control the pace of the delivery of the head. Maternal pushing is often helpful, but too forceful pushing can cause the head to deliver precipitously and can lead to perineal lacerations.

After the head is delivered, the fetal neck is checked for a nuchal cord. Routine suctioning of the nares is no longer recommended by the American Academy of Pediatrics. However, in infants who are likely to require resuscitation, suctioning may be necessary. With both hands on the head, a gentle posterior traction is applied at an angle of 45° to deliver the anterior shoulder followed by gentle anterior traction of the head to deliver the posterior shoulder. Oxytocin is often started at delivery of the anterior shoulder. Continue to support the head with one hand and use other hand to deliver the body. The cord is clamped at two locations, several centimeters apart and cut between the clamps. There has been increasing data over the past few years suggesting benefits for delayed cord clamping. It has been shown to decrease anemia in term infants. Delayed cord clamping is defined as 2–3 min after delivery [22]. The infant is cleaned or placed directly with the mother, assuming a normal appearance and Apgar evaluation. Encouraging skin-to-skin contact between mother and newborn as much as possible is recommended.

Placental separation is evidenced by an increase in the length of umbilical cord, a bolus of blood from the uterus, and migration of superior border of the uterus within the abdomen with an increase in uterine firmness.

Placental delivery is facilitated by applying gentle traction on the umbilical cord with one hand and a gentle counter traction with a vertical pressure just superior to the pubic symphysis with the other hand to prevent inversion of the uterus.

Intravenous oxytocin is administered for the prevention of postpartum hemorrhage. The placenta is examined for its completeness and the uterus is manually explored if the placenta is not intact.

Retained placental fragments increase the risk of postpartum hemorrhage. The mother is examined for cervical, vaginal, or perineal tears. First degree tears or hemostatic abrasions usually do not require suturing.

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Medical Problems During Pregnancy 11

Matthew Halfar

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Introduction

Many acute and chronic medical conditions can expose both the pregnant patient and her developing fetus to risk of poor outcomes. Certain medical conditions can have dire consequences for the mother or fetus if not recognized and treated expeditiously. Family physicians should prioritize preconception counseling, preventative measures, and patient education to minimize the risk of harm to both the pregnant patient and fetus. Commonly encountered medical problems and urgent issues seen less commonly in pregnancy will be discussed in this chapter.

Respiratory Disorders

Asthma

The goal of treatment of asthma in pregnancy is to maintain adequate oxygenation to the developing fetus. The risks of suboptimal control include preeclampsia, gestational diabetes, placental abruption, placenta previa, obstetric hemorrhage, caesarean birth, preterm delivery, and small for gestational age (SGA) infants [1, 2]. Excellent outcomes are achievable with optimal control. Roughly one-third of patients will have worsening severity of asthma during pregnancy. Level of control is typically measured by the patient's forced expiratory volume in the first second of expiration (FEV_1) and peak expiratory flow (PEF). Classification of asthma severity and asthma control should be done in the same manner as the nonpregnant population. The severity of a patient's asthma is directly related to exacerbation and hospitalization rates [2]. For mild, intermittent asthma, controller medication is not indicated. Short-acting β2-agonists as rescue treatment may be used as needed. The cornerstone of treatment for persistent asthma is stepwise titration of inhaled corticosteroids (ICS) and long-acting beta agonists (LABA). Up-titration of the ICS dose may be considered in lieu of adding a LABA in moderate persistent and severe persistent asthma [1]. Budesonide (Pulmicort) has the most robust safety profile to date, though other ICS formulations are considered safe. Avoidance of triggers and control of atopy, rhinitis, and gastroesophageal reflux disease reduces the risk of an exacerbation. Exacerbations are treated in the same manner as the nonpregnant population.

Influenza

Vaccination against influenza is an important part of prenatal care. Influenza during pregnancy increases the risk of maternal and fetal morbidity and mortality. Inactivated influenza vaccines may be safely administered at any point during pregnancy. Live attenuated vaccines, such as the nasal influenza vaccine, are not recommended. Pregnant patients with a history of egg allergy manifesting as hives may safely receive the vaccine. In the event that more serious reactions have occurred due to exposure to eggs, the vaccine may be administered in a medical setting capable of managing anaphylaxis. In the event that a pregnant patient presents within 48 h of onset of influenza-like illness, treatment with oseltamivir (Tamiflu) 75 mg orally twice daily for 5 days or zanamivir (Relenza Diskhaler) two inhalations

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twice daily for 5 days) is recommended [3]. Antiviral treatment may be initiated at >48 h from the onset of symptoms in the event of severe illness. The decision to treat with an antiviral agent should be based on clinical judgment, regardless of the results of influenza testing, due to the possibility of false-negative results. Pregnant patients treated for influenza in the outpatient setting should have close follow-up due to the increased risk of pneumonia following influenza infection.

Cardiovascular Disease

Chronic Hypertension

Chronic hypertension (CHTN) in pregnancy is defined as hypertension diagnosed prior to pregnancy or prior to 20 weeks gestation. Maternal risks of hypertension in pregnancy include cerebrovascular accident, pulmonary edema, renal failure, myocardial infarction, and death. CHTN increases the risk of preeclampsia, gestational diabetes, placental abruption, postpartum hemorrhage, and cesarean delivery, as well. Fetal risks include low birth weight, stillbirth, preterm birth, and congenital anomalies. The American College of Obstetrics and Gynecology (ACOG) defines hypertension as a systolic blood pressure (SBP) measurement of 140 mmHg or greater, or a diastolic blood pressure (DBP) of 90 mmHg or greater, measured on two occasions at least 4 h apart. Severe-range hypertension is defined as either an SBP of 160 mmHg or greater, or a DBP of 110 mmHg or greater, or both. Laboratory evaluation of liver function, kidney function, and a complete blood count should be completed at the time of diagnosis. A random urine protein-to-creatinine ratio may be necessary at baseline as women with CHTN may have proteinuria. Differentiation of CHTN with proteinuria and CHTN with superimposed preeclampsia can be challenging and may require consultation with a maternal-fetal medicine specialist [4].

ACOG recommends initiating medication treatment for CHTN when either the SBP is 160 mmHg or greater, or the DBP is 110 mmHg or greater. For acute-onset severe-range hypertension, treatment should be initiated as soon as possible. Urgent evaluation and treatment of severe-range hypertension on a labor and delivery unit is appropriate. Labetalol, hydralazine, and nifedipine (Procardia) are the most commonly used medications to treat hypertension in pregnancy. Because up to 50% of women with CHTN may develop preeclampsia, pregnant women with CHTN should be started on low-dose aspirin at 81 mg/day at 12–28 weeks gestation, ideally prior to 16 weeks, and this should be continued until delivery. Antenatal surveillance for patients with CHTN may be beneficial, though evidence of the ideal time to initiate testing, the modality of testing and the frequency of testing is lacking. For women with CHTN not requiring medication management and lacking indications for earlier delivery, delivery prior to 38 0/7 weeks is not recommended. For women with CHTN that require medication to control blood pressure and are otherwise without complications, delivery prior to 37 0/7 weeks is not recommended. Because of the increased risk of developing superimposed preeclampsia with advancing gestational age, the risks and benefits of delivery beyond 39 0/7 weeks should be carefully considered and discussed with the patient [4].

Infectious Disease

Urinary Tract Infection

Physiological changes of pregnancy increase the risk of urinary tract infection (UTI). UTIs in pregnancy may present as asymptomatic bacteriuria (ASB) or symptomatic disease with cystitis and/or pyelonephritis. Bacteriuria, including ASB, increases the risk of pyelonephritis and, possibly, preterm birth and decreased birth weight [5]. Pyelonephritis increases the risk of anemia, acute kidney injury, sepsis, pulmonary insufficiency, and acute respiratory distress syndrome in pregnant women [6]. ASB is defined by the Infectious Diseases Society of America (IDSA) as greater than 10^5 colony forming units (CFUs) per milliliter (mL) of the same bacteria on two voided specimens or greater than 10^2 CFUs/mL on one catheterized specimen [5]. The United States Preventive

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Services Task Force (USPSTF) recommends one urine culture between 12 and 16 weeks gestation. The American College of Obstetricians and Gynecologists (ACOG) recommends one urine culture early in pregnancy (Table 1). Neither organization clarifies whether a second urine culture should be collected prior to treatment. Treatment for ASB is only indicated for a positive urine culture with a colony count greater than 10^5 CFUs/mL [5]. ASB with group B streptococcus (GBS) isolated on urine culture should be treated in the same manner. However, GBS bacteriuria at any colony count during pregnancy is an indication for intrapartum GBS prophylaxis [7].

Pregnant women diagnosed with pyelonephritis should be admitted to the hospital for intravenous antibiotics [6]. Empiric treatment for presumed cystitis with classic symptoms is recommended while awaiting culture and sensitivity to direct final treatment. The typical duration of treatment for both ASB and symptomatic cystitis is 4–7 days [6]. Consideration of local antimicrobial resistance and medication safety profiles should guide treatment. Medications such as penicillins, cephalosporins, macrolides, and clindamycin are generally considered safe in pregnancy.

There is mixed evidence on the association of birth defects and exposure to nitrofurantoin (Macrobid, Macrodantin) or sulfonamides during fetal organogenesis. Caution is also advised with use of nitrofurantoin or sulfonamides within 30 days of birth due to a possible increased risk of neonatal jaundice. Both of these medications are contraindicated in women with glucose-6-phosphate dehydrogenase deficiency [8].

Table 1 Infectious disease screening in pregnancy

Recommended test	Timing
HIV	Initial prenatal visit
Hepatitis B	Initial prenatal visit
Syphilis	Initial prenatal visit
Urine culture	Initial prenatal visit (ACOG) 12–16 weeks gestation (USPSTF)
Varicella	Titer at initial visit if no documented history of disease or adequate vaccination
Hepatitis C	Initial prenatal visit if indicated by risk factors
Group B streptococcus	Routinely after 35 weeks gestation or as indicated

HIV

Pregnant women should be tested for HIV as early as possible during each pregnancy (Table 1) [9]. More than 90% of children infected with HIV in childhood acquire the disease in utero, during delivery or through breastfeeding [10]. The risk of mother-to-child transmission (MTCT) can be greatly reduced with combined antiretroviral therapy (cART). In all patients infected with HIV, the objective of cART is to reduce the plasma level of HIV RNA to an undetectable level. In antiretroviral (ARV)-naïve pregnant patients, cART should be started as early as possible. Pregnant women already on a full cART regimen should, in general, continue with their prescribed regimen. Providers should seek consultation or guidance, if necessary, regarding optimal medication regimens that achieve viral suppression while reducing fetal and maternal risk. The United States Department of Health and Human Services' AIDSinfo website (https://aidsinfo.nih.gov/) includes updated guidelines on treatment of HIV in pregnant patients with guidance on choosing an appropriate medication regimen. Also, the National Perinatal HIV Hotline (1-888-448-8765) provides clinical consultations for providers caring for patients with HIV and their children. Patients should be counseled on the importance of daily adherence to their medication regimen. Providers should report patient exposures to antiretroviral therapy to the Antiretroviral Pregnancy Registry (http://www.apregistry.com/). Retesting for HIV in the third trimester, before 36 weeks gestation, is recommended in patients at high risk of acquiring HIV (Table 2). It is recommended that infants exposed to HIV receive antiretroviral medications. Because it is recommended to start antiretroviral therapy as soon as possible after birth, delivery planning should include an evaluation of the delivering hospital's ability to care for HIV-exposed infants [11].

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Table 2 Risk factors for HIV and HCV infection in pregnancy

Risk factors for HIV infection	Risk factors for HCV infection
Unprotected anal/vaginal sexual intercourse	History of tattoos/piercings done with unsterilized instruments
History of sexually transmitted infections	History of HIV infection
History of injection drug use/sharing needles	History of injection drug use/sharing needles
Incarceration	History of intranasal drug use
Sex work	Incarceration
Occupational exposure	Occupational exposure
History of blood transfusion prior to 1992	History of blood transfusion prior to 1992

Viral Hepatitis

Hepatitis A

Hepatitis A virus (HAV) produces a self-limited symptomatic or asymptomatic infection that often requires supportive care only. Children are typically asymptomatic when infected but can still transmit the virus [12]. Fecal-oral transmission is facilitated by poor hygiene and substandard sanitation. Detection of immunoglobulin M (IgM) antibodies to HAV are diagnostic of the infection. The vaccine may be given during pregnancy if the patient is at increased risk or desires to be vaccinated [13]. Pregnant patients should be offered postexposure prophylaxis and active vaccination if they report HAV exposure [12].

Hepatitis B

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide [12]. HBV can be transmitted through sexual or parenteral contact. However, up to 50% of HBV infection worldwide is attributable to perinatal transmission. While Hepatitis B virus (HBV) more commonly leads to resolved infection and immunity if acquired in adulthood, 90% of exposed neonates will eventually develop chronic HBV infection in the absence of adequate immunoprophylaxis [14]. The USPSTF recommends that all pregnant women be screened for HBV surface antigen (HBsAg) as early as possible in pregnancy (Table 1) [15]. If HBV screening is negative and the patient is determined to be HBV nonimmune, the HBV vaccine may be given during pregnancy if the patient is at increased risk or desires to be vaccinated [13]. The Society for Maternal-Fetal Medicine (SMFM) recommends HBV viral load testing in the third trimester for pregnant patients with a positive HBsAg test or patients known to be chronic carriers. Tenofovir is recommended for the duration of pregnancy as the first-line antiviral agent if the HBV viral load is greater than 6–8 log 10 copies/mL [14]. HBV immunoglobulin and the HBV vaccine should be administered to all infants born to HBsAg-positive or HBsAg-unknown mothers within 12 h of birth.

Hepatitis C

Hepatitis C virus (HCV) is the leading cause of chronic liver disease in the United States [12]. Mother-to-child transmission (MTCT) is the leading cause of HCV infection in children. The risk of MTCT per pregnancy is 4–7% [16]. The risk of transmission is higher if the mother is co-infected with HIV. MTCT is thought to occur only with detectable HCV RNA during pregnancy [16]. It is recommended that pregnant women at high risk of HCV infection be screened for anti-HCV antibodies during pregnancy (Tables 1 and 2) [12]. Currently, antiviral medications recommended for treatment of HCV are not approved for use in pregnant women. Infants born to mothers infected with HCV should be screened for anti-HCV antibodies after 18 months of age or for HCV RNA after 1 month of age [17].

Cervicitis

Pregnant women with cervicitis should be evaluated for *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (CT), and *Trichomonas vaginalis*. Primary herpes simplex virus (HSV) may also cause cervicitis [18].

Nucleic acid amplification testing (NAAT) on an endocervical swab, a vaginal swab, or a urine

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sample reliably detects GC and CT. If urine sampling is elected, the patient should be instructed on collecting a first-void sample, also known as a "dirty" catch. Trichomonads may be detected on wet-prep microscopy. Because the sensitivity of detecting trichomonads on microscopy is 50%, further testing should be pursued if cervicitis persists in the absence of positive NAAT testing for GC or CT [18]. Confirmatory testing for suspected HSV includes viral detection via viral culture or polymerase chain reaction (PCR), or antibody detection via serological testing [19].

Chlamydia, gonorrhea, and trichomonas infections are managed in the same manner as nonpregnant patients. Although tests-of-cure are not recommended, retesting may be appropriate if there are concerns with reinfection or adherence.

Genital Herpes Simplex

Transmission of herpes simplex virus (HSV) in utero or during birth can lead to poor outcomes in affected neonates. The route of delivery is dependent on the presence of active vaginal or vulvar lesions or prodromal symptoms at the time of labor and delivery. Suppressive therapy with acyclovir (Zovirax) 400 mg three times per day or valacyclovir (Valtrex) 500 mg two times per day, starting at 36 weeks gestation, has been shown to reduce the risk of recurrence of active disease at the time of delivery [19]. Active HSV in a pregnant patient should be managed in the same manner as the nonpregnant population. The Centers for Disease Control's (CDC) 2015 Sexually Transmitted Disease Treatment Guidelines offer guidance on effective medication regimens and may be found here: https://www.cdc.gov/std/tg2015/herpes.htm.

Syphilis

From 2013 to 2017, cases of congenital syphilis in the United States increased by 53.3% [20]. The risks of untreated maternal syphilis include low birth weight, congenital syphilis, preterm birth, stillbirth, and neonatal death [21]. Universal screening of pregnant women for syphilis at the initial prenatal visit is recommended by the USPSTF (Table 1) [22]. Penicillin G is the only known effective antibiotic to treat fetal syphilis and to prevent maternal transmission. For pregnant women with a major penicillin allergy, the CDC recommends penicillin desensitization and subsequent treatment. CDC recommendations on evaluation and treatment of syphilis during pregnancy may be found here: https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm. Referral to a maternal-fetal medicine specialist is appropriate, especially with advancing gestational age, but referral should not delay treatment.

Varicella Zoster

Varicella zoster virus (VZV) is highly contagious. Immune status against VZV should be verified by either a history of chickenpox, a history of completed vaccination or by serology (Table 1). Varicella pneumonia has been reported to develop in 10–20% of pregnant women who acquire VZV with a mortality rate among patients with pneumonia reported to be 10–40% [23, 24]. While rare, congenital varicella infection can cause fetal skin scarring, chorioretinitis, limb hypoplasia, and microcephaly [23]. In the event of uncomplicated primary VZV infection in a pregnant woman, treatment with acyclovir (Zovirax) 800 mg five times per day for 5–7 days is recommended. Varicella nonimmune patients who report a significant exposure to VZV should receive VZV immunoglobulin within 96 h of exposure [24]. The varicella vaccine is contraindicated in pregnancy.

Tuberculosis

Untreated tuberculosis (TB) in pregnancy increases the risk of preeclampsia, postpartum hemorrhage, spontaneous abortion, preterm birth, and low birth weight infants [25]. Pregnant patients at high risk of infection (Table 3) with TB should be screened with a tuberculin skin test (TST). In patients with HIV or previous BCG

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Table 3 Risk factors and degree of risk for development of tuberculosis

Risk factors	Degree of risk
Close contact with a person with infectious tuberculosis	High
HIV	High
Homelessness	Moderate
Injection drug use	Moderate
Occupational exposure in high risk facilities (hospitals, skilled nursing facilities, correctional facilities, homeless shelters)	Moderate
Immigration from an area of the world with high rates of tuberculosis	Moderate
Diabetes mellitus	Low
Smoking	Low

vaccination, an interferon-gamma release assay (IGRA) may reduce the risk of a false-negative or false-positive TST, respectively [25].

A systematic review of latent tuberculosis infection (LTBI) in pregnancy demonstrated a prevalence of 14–48% among various cohorts in the United States [26]. The CDC recommends treatment for active TB and LTBI as soon as TB is detected. For patients with active TB, the recommended regimen is isoniazid, rifampin, and ethambutol daily for 2 months, then isoniazid and rifampin daily or twice weekly for 7 months, thereafter. For patients with LTBI, isoniazid daily or twice weekly for 9 months and pyridoxine (B6) supplementation is recommended. CDC recommendations for treatment of TB in pregnancy may be found here: https://www.cdc.gov/tb/topic/populations/pregnancy/default.htm.

Endocrine Disorders

Diabetes Mellitus

Pregestational Diabetes

Pregestational diabetes is defined as type 1 or type 2 diabetes diagnosed either prior to conception or early in pregnancy. Because of the significant risks that hyperglycemia imposes on both a pregnant woman and her fetus, more frequent monitoring is often necessary and referral to a maternal-fetal specialist may be appropriate. Women with type 1 or type 2 diabetes who are planning to become pregnant should receive preconception counseling on the importance of euglycemic control to reduce the risk of maternal and fetal complications. At least 400mcg daily of folic acid should also be prescribed due to the increased risk of neural tube defects in the infants of women with diabetes [27].

Throughout pregnancy, there is a physiologic increase in insulin resistance in all pregnant women. Pregnant women with diabetes should be advised to check their blood glucose after fasting and 1 or 2 h postprandial throughout their pregnancy. The following glucose levels should be targeted when considering medication adjustment: less than or equal to 95 mg/dL for the fasting value and less than or equal to 140 mg/dL for the 1-h postprandial value or 120 mg/dL for the 2-h postprandial value. Because of the increased risk of developing preeclampsia, pregnant women with pregestational diabetes should be started on low-dose aspirin at 81 mg/day at 12–28 weeks gestation, ideally prior to 16 weeks, and this should be continued until delivery [27]. Fetal growth should be monitored with fundal height measurement. Periodic ultrasound assessment of growth in the third trimester is a common practice and may be considered, especially if there are concerns for fetal growth restriction or macrosomia. Antenatal surveillance is recommended starting at 32 weeks gestation.

Insulin is the preferred treatment for pregestational diabetes. A 2017 Cochrane review reported insufficient data to recommend any specific insulin regimen over another in pregestational diabetes [28]. The safety of oral antidiabetic medications in the treatment of pregestational diabetes has not been well studied. The decision to prescribe oral antidiabetic medications should be individualized and should include a thorough discussion of the risks and benefits of use [27].

Gestational Diabetes

Screening for gestational diabetes (GDM) is recommended between 24 and 28 weeks gestation. Nearly all obstetricians in the United

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States use the 1-h oral glucose tolerance test (OGTT) as a screening tool [29]. Institutional thresholds for a positive screen vary between 130 mg/dL and 140 mg/dL. A positive 1-h OGTT is typically followed by a confirmatory 3-h OGTT with two or more abnormal values being diagnostic for GDM. Blood sugar testing recommendations and thresholds for treatment are the same as in pregestational diabetes.

Diet and exercise improve glucose levels and medication may not be necessary in GDM [29]. Diet-controlled GDM is classified as A1GDM whereas GDM requiring medication to maintain normal glucose levels is classified as A2GDM. As in pregestational diabetes, insulin is the preferred treatment for poorly controlled GDM. Use of oral antidiabetic medications should be prescribed on an individualized basis in situations where compliance, patient preference, or logistical difficulties complicate adherence to an insulin regimen. ACOG states that metformin and "rarely glyburide" are reasonable alternatives to insulin therapy provided patients are informed of the limitations of safety data and the risk of treatment failure. Antenatal surveillance may be beneficial for patients with poor glucose control and A2GDM. There is no consensus regarding antenatal surveillance for patients with well-controlled A1GDM [29].

Because GDM significantly increases the risk that a woman will develop diabetes later in life, it is recommended that screening with a 75 g, 2-h OGTT be performed at 4–12 weeks postpartum. Thereafter, screening for diabetes every 1–3 years is recommended by the American Diabetes Association and ACOG [29].

Thyroid Disorders

Thyroid stimulating hormone (TSH) values vary during pregnancy due to normal physiologic changes and should be taken into account when interpreting thyroid studies. Notably, an increase in human chorionic gonadotropin (hCG) during the first trimester weakly stimulates TSH receptors on the thyroid gland leading to a slight increase in free T_4 secretion and a subsequent decrease in TSH. TSH values normalize after the first trimester and subsequently increase progressively through the second and third trimesters. The American Thyroid Association has published the following trimester-specific reference ranges for TSH: 0.1–2.5 mIU/L in the first trimester; 0.2–3.0 mIU/L in the second trimester; and 0.3–3.0 mIU/L in the third trimester. A 30% enlargement of the thyroid gland is typical during pregnancy [30]. Significant derangements in free T_4 or T_3 values outside of the reference range are not expected physiological changes of pregnancy and should be correlated with clinical symptoms to evaluate for overt hypothyroidism or hyperthyroidism.

Hypothyroidism

Untreated maternal hypothyroidism is associated with spontaneous abortion, preeclampsia, preterm birth, placental abruption, fetal loss, low birth weight, and impaired neuropsychological development of affected children. Clinical signs and symptoms of hypothyroidism include fatigue, weight gain, constipation, cold intolerance, muscle cramps, dry skin, and hair loss. Hypertension may also be noted. Lab findings of overt hypothyroidism include elevated TSH, decreased free T_4, and, in the case of Hashimoto thyroiditis, the presence of antithyroid peroxidase antibodies. The preferred treatment for hypothyroidism in pregnancy is levothyroxine at an initial dosage of 1–2 mcg/kg daily. TSH should be measured at 4–6 week intervals and levothyroxine adjusted until the TSH value reaches a normal level. There is insufficient evidence to recommend treatment of subclinical hypothyroidism despite some studies showing an association with adverse perinatal outcomes [30].

Hyperthyroidism

Clinical signs and symptoms of overt hyperthyroidism include heat intolerance, diarrhea, tremors, anxiety, excessive sweating, tachycardia, weight loss, goiter, palpitations, insomnia, and hypertension. Untreated hyperthyroidism is associated with low birth weight infants and, possibly, fetal loss [30]. Lab findings of hyperthyroidism include a decreased TSH level and an elevated free T_4 level. Graves' disease accounts for the great majority of cases of overt hyperthyroidism

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and is confirmed by the presence of thyroid-stimulating immunoglobulin (TSI). Historically, propylthiouracil (PTU) has been the treatment of choice for hyperthyroidism in pregnancy due to teratogenic effects of methimazole (Tapazole) during the first trimester. However, in 2009, the U.S. Food and Drug Administration (FDA) issued a safety alert for PTU due to reports of hepatotoxicity. Consequently, the American Thyroid Association and the American Association of Clinical Endocrinologists recommended that PTU be used in the first trimester only and that treatment be switched to methimazole for the remainder of the pregnancy [30, 31]. Due to an increased risk of fetal thyrotoxicosis in pregnancies of women with Graves' disease, referral to a maternal-fetal specialist may be appropriate [30].

Hematologic Disorders

Iron Deficiency Anemia

In pregnancy, anemia is defined as a hemoglobin or hematocrit level below the following trimester-specific thresholds: 11.0 g/dL or 33%, respectively, in the first trimester; 10.5 g/dL or 32%, respectively, in the second trimester; and 11.0 g/dL or 33%, respectively, in the third trimester. The Institute of Medicine recommends that thresholds be lowered by 0.8 g/dL for hemoglobin and 2% for hematocrit in African-American adults [32]. ACOG recommends that all women be screened for anemia during pregnancy. The most common cause of anemia during pregnancy is iron deficiency anemia (IDA). IDA is commonly diagnosed by the presence of low ferritin levels in the setting of a microcytic, hypochromic anemia. IDA in pregnancy is associated with low birth weight, preterm delivery, and perinatal mortality [32].

There is insufficient evidence regarding the optimal dose or formulation of elemental iron for supplementation (Table 4). The British Society of Hematologists suggests 40–80 mg of elemental iron orally once daily at initiation of treatment. Response can be evaluated 2–3 weeks after starting medication and the dose adjusted if necessary. Supplementation should continue until at least 6 weeks postpartum [33]. In patients that do not respond to oral iron, cannot tolerate oral iron, or need rapid correction due to advancing gestation, intravenous iron is an option. A 2019 meta-analysis concluded that IV iron is more efficacious at reaching target hemoglobin levels with greater speed and fewer side effects [34].

Table 4 Different formulations of iron supplementation

Oral iron formulations	IV iron formulations
Ferrous sulfate	Iron dextran
Ferrous gluconate	Iron sucrose
Ferrous fumarate	Ferric carboxymaltose

Gestational Thrombocytopenia

Gestational thrombocytopenia (GT) is defined as a platelet count below 150 x 10^9/L. GT typically does not present before the midpoint of the second trimester and accounts for about 75% of cases of thrombocytopenia in pregnancy. In 1–5% of women, platelet counts in GT are observed to be less than 100 x 10^9/L and rarely less than 75 x 10^9/L [35]. GT generally does not affect the health of the mother or her newborn, though, in rare cases, mild thrombocytopenia can be observed in infants born to mothers with GT [36]. However, because GT is a diagnosis of exclusion, other causes of thrombocytopenia should be considered and referral to a hematologist may be appropriate. After 20 weeks gestation, in the setting of thrombocytopenia, it is essential that preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy are considered as part of the differential diagnosis.

Venous Thromboembolism

Pregnant women and women in the postpartum period are 4–5 times more likely to develop venous thromboembolism (VTE) than non-pregnant women due to increased venous stasis, a hypercoagulable state, compression of the inferior vena cava, alteration of coagulation factors, and decreased mobility [37]. Every pregnant woman should be asked about a personal or family history of thromboembolism and abnormal bleeding or clotting disorders.

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Deep vein thrombosis (DVT) accounts for the majority of VTE events in pregnancy. If DVT is clinically suspected, compression ultrasonography of the proximal veins is recommended as the initial test due to the increased frequency of iliofemoral and iliac vein thromboses when compared to nonpregnant women [37]. Because of the decreased sensitivity and specificity of D-dimer as a screening test in pregnancy, it is not recommended as part of the evaluation of VTE.

Pulmonary embolism (PE) in pregnancy is diagnosed with either ventilation-perfusion (VQ) scanning or computed tomographic angiography (CTA). In general, fetal exposure to radiation from both tests is low, though fetal absorption of radiation is slightly higher with VQ scanning than with CTA. Maternal exposure to radiation, particularly to the breast, is lower with VQ scanning. Guidelines from the American Thoracic Society and the Society of Thoracic Radiology suggest that chest x-ray (CXR) be used as an initial test followed by VQ scanning if the CXR is normal and CTA if the CXR is abnormal [37].

The recommended treatment for VTE in pregnancy is subcutaneous low-molecular-weight heparin at a therapeutic dose, though consultation with cardiology and maternal-fetal medicine is recommended for pregnant women with mechanical heart valves. Oral direct thrombin inhibitors and anti-Xa inhibitors should be avoided in pregnancy. Guidelines from the American College of Chest Physicians on duration of therapy may be found here: https://journal.chestnet.org/article/S0012-3692(15)00335-9/fulltext. ACOG recommends that therapy be continued until at least 6 weeks postpartum irrespective of the clinical scenario [37].

Neurologic Disorders

Epilepsy

Infants born to mothers with epilepsy are at increased risk of congenital malformations. The majority of this risk is conferred by antiepileptic drug (AED) use during pregnancy, though convulsive seizures in the first trimester can increase the risk of malformations, as well [38]. Most women with epilepsy will require continued medication treatment throughout pregnancy. A 2016 Cochrane review of AED monotherapy concluded that valproate has the highest risk of malformations at 10.93%, while levetiracetam and lamotrigine appear to be associated with the lowest levels of risk [39].

Migraine Headache

The frequency and severity of migraine headaches typically decrease during pregnancy. However, treatment may still be necessary for prophylaxis or acute migraine headaches. For prophylaxis, propranolol (Inderal) is generally considered safe in pregnancy, though there are reports of fetal growth restriction associated with fetal propranolol exposure. Valproic acid (Depakote) and topiramate (Topamax) should be avoided in pregnancy [40]. Acetaminophen (Tylenol) and metoclopramide (Reglan) are the only medications considered safe for treatment of acute migraine headaches. While the safety profile of sumatriptan (Imitrex) use in pregnancy is encouraging, its use should be reserved for severe headaches not responsive to other treatments due to an association between use in the second or third trimester and postpartum hemorrhage [41].

Musculoskeletal Disorders

Low Back Pain

More than 70% of pregnant women will experience low back pain at some point during their pregnancy [42]. A 2007 Cochrane review of eight studies concluded that low back pain was reduced with both individual (number needed to treat [NNT] = 2.1) and group physical therapy (NNT = 3.2), and that disability as measured in days of sick leave was reduced by 12% [43]. A 2015 Cochrane review of interventions for low back pain and pelvic pain concluded that land-based exercise interventions of varying duration

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lasting at least 5 weeks significantly reduced low back pain and sick leave [44].

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) in pregnancy is thought to be the result of physiologic changes during pregnancy that result in fluid retention and subsequent median nerve compression [45]. The natural history of pregnancy-associated CTS is variably reported [42, 45]. Evaluation of CTS in pregnancy is the same as in the nonpregnant population, and while there is limited guidance on the indications for electrodiagnostic studies during pregnancy, nerve conduction studies and electromyography are not contraindicated. As in the nonpregnant population, treatment for CTS should be guided by the severity of discomfort and disability, taking into account that the majority of cases resolve within 2–4 weeks of delivery [42].

Psychiatric Disorders

Depression

Up to 23% of pregnant women may experience depression during pregnancy. Some studies have reported an increased risk of low birth weight (LBW) infants, small for gestational age (SGA) infants and preterm delivery when the mother was affected by depressive symptoms. Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have been shown to be beneficial for treatment of mild-to-moderate depression in pregnancy [46]. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medication in women who have failed to respond to CBT or IPT. Some studies reporting associations between SSRIs and outcomes of offspring such as growth effects, malformations, and neurobehavioral effects have been confounded by lack of adequate controls. Women should, however, be counseled that 15–30% of infants exposed to SSRIs in utero may have increased irritability and restlessness that typically resolves by 2 weeks of age. Also, data showing a possible link between paroxetine and cardiac malformations resulted in the United States Food and Drug Administration classifying paroxetine as a category "D" drug [46]. In pre-conceptional and pregnant women taking paroxetine, the decision to switch to a different medication should be carefully considered and discussed with the patient. Ultimately, severity of depression, the safety profile of psychotropic medications, and gestational age should guide decisions regarding any treatment or the decision to consult with a psychiatrist.

Special Considerations

Substance Use Disorders

ACOG advocates for screening for substance use in pregnancy followed by intervention and referral, if necessary. There are multiple screening tools available: the six-question "Wayne Indirect Drug Use Screener" shows a strong association with toxicology results, and the three-question "Substance Use Risk Profile-Pregnancy" has been validated in pregnancy (Table 5) [47]. Interventions for positive screens include counseling on the effects of substance use during pregnancy, drug treatment services, and coordination of a multidisciplinary treatment team.

Obesity

Obesity in pregnancy confers an array of risks to the well-being of a mother and her fetus. The World Health Organization has defined obesity by a body mass index (BMI) of 30.0 kg/m^2 or greater and further divides obesity into three classes (Table 6). Fetal risks include neural tube defects, hydrocephaly, cardiovascular anomalies, and death. There is also an increased risk of neonatal and infant death in the offspring of obese mothers. Maternal risks include stillbirth, cardiac dysfunction, nonalcoholic fatty liver disease, gestational diabetes mellitus, preeclampsia, cesarean delivery, endometritis, impaired wound healing,

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Table 5 Screening tools for substance abuse

Wayne Indirect Drug Use Screener (true/false)	Substance Use Risk Profile-Pregnancy
1. I am currently married	1. Have you ever smoked marijuana?
2. In the past year, I have been bothered by pain in my teeth or mouth	2. In the month before you knew you were pregnant, how many beers, how much wine, or how much liquor did you drink?
3. I have smoked at least 100 cigarettes in my entire life	3. Have you ever believed that you needed to cut down on your drug (including the nonmedical use of prescription medications) or alcohol?
4. Most of my friends smoke cigarettes	
5. There have been times in my life, for at least 2 weeks straight, where I felt like everything was an effort	
6. I get mad easily and feel a need to blow off some steam	

Wayne Indirect Drug Use Screener: 1 point for each "True" response with increasing likelihood of positive toxicology screens with higher scores.
Substance Use Risk Profile-Pregnancy: 1 point for each answer of "yes" on questions 1 or 3, and 1 point for an answer of "2 or more alcoholic drinks" on question 2; Interpretation: 0 = low risk, 1 = moderate risk, and 2 = high risk.

Table 6 World Health Organization weight classification

Body mass index (kg/m^2)	Classification
$<$18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
30.0–34.9	Class I obesity
35.0–39.9	Class II obesity
$\geq$ 40.0	Class III obesity

Data obtained from the World Health Organization (WHO) [Internet]. Retrieved 29 March 2020. Available from: https://www.who.int/health-topics/obesity

and venous thromboembolism [48]. The risk of complications increases with increasing BMI. Weight loss prior to pregnancy is the most effective intervention to reduce the risk of complications during pregnancy as weight loss or inadequate weight gain may result in poor neonatal outcomes [48]. Recommendations by the National Academy of Medicine (formerly the Institute of Medicine) on weight gain during pregnancy may be found here: https://www.nap.edu/resource/12584/Report-Brief%2D%2D-Weight-Gain-During-Pregnancy.pdf.

In addition to standard prenatal care, ACOG recommends that obese pregnant women be counseled on the limitations of ultrasonography to detect congenital anomalies and that an early screen for gestational diabetes be performed for women with a BMI of 30.0 or greater [48].

Bariatric Surgery and Pregnancy

Periodic evaluation for nutritional deficiency following Roux-en-Y gastric bypass surgery is recommended in the nonpregnant population and should be considered during pregnancy, as well. The most common nutrient deficiencies following gastric bypass involve protein, iron, vitamin B_{12}, folate, vitamin D, and calcium. If initial evaluation is reassuring, surveillance of the blood count, iron, ferritin, calcium, and vitamin D every trimester may be considered [49]. Consideration should also be given to involving the patient's bariatric surgery team in prenatal care as this may be of benefit to maintaining appropriate weight gain during pregnancy [50] and may assist in evaluation of potential complications related to the surgery that become apparent during pregnancy.

Diagnostic Imaging During Pregnancy

Magnetic resonance imaging (MRI) and ultrasonography do not confer risk of radiation exposure and are the preferred imaging techniques in pregnancy. However, the great majority of imaging protocols with computed tomography (CT), x-rays, or nuclear medicine modalities are performed at radiation doses much lower than thresholds associated with fetal harm. The

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Selected Practice Recommendations of the American College of Radiology on ionizing radiation in pregnant or potentially pregnant women may be found here: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Pregnant-Pts.pdf.

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Obstetric Complications During Pregnancy

12

Jeffrey D. Quinlan

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There are a wide range of obstetric complications that may occur during pregnancy. This chapter will focus on six of the most common complications including spontaneous abortion, ectopic pregnancy, hypertensive disorders of pregnancy, placenta previa, and preterm labor.

Spontaneous Abortion

Spontaneous abortion is defined as the involuntary loss of pregnancy prior to 20 weeks of gestation.

Vaginal bleeding in the first trimester of pregnancy is common. It may occur as a result of spontaneous abortion, ectopic pregnancy, gestational trophoblastic disease, or cervical causes. Approximately half the pregnancies complicated by first trimester bleeding result in viable pregnancies.

Epidemiology

Spontaneous abortion or miscarriage occurs in about 15% of clinically identified pregnancies and may occur in up to 50% of pregnancies prior to clinical identification [1].

Etiology

The cause of spontaneous abortion is rarely identified in the individual patient. Research has demonstrated, however, that approximately half of miscarriages occur as a result of trisomy, triploidy, monosomy, or another significant genetic abnormality [2]. Additionally, several environmental factors have been associated with miscarriage including both internal and external factors. Internal factors include advanced maternal age, uterine anomalies, leiomyomata, incompetent cervix, and luteal phase defects that lead to progesterone deficiency. External factors include substance use such as tobacco, alcohol, and cocaine, radiation exposure, infections, and occupational chemical exposure to substances such as arsenic, benzene, ethylene oxide, formaldehyde, or lead.

Diagnosis

Women experiencing a spontaneous abortion typically present with vaginal bleeding and cramping. They may also report a diminution or reversal of early pregnancy symptoms (fatigue, nausea, breast tenderness).

The first steps in evaluation of a patient with suspected miscarriage are to obtain vital signs and establish an estimated gestational age based on last menstrual period. If the estimated gestational age is greater than 9 weeks, an attempt should be made to auscultate fetal heart tones. Examination should then include abdominal, speculum, and pelvic examinations. If adnexal tenderness is identified, ectopic pregnancy should be considered. Non-uterine causes of bleeding can be identified during the speculum examination as can the presence or absence of cervical dilation. The diagnosis of spontaneous abortion can be assisted by use of transvaginal ultrasound. A completed spontaneous abortion will present with an empty uterus with an echogenic endometrial stripe. In a viable gestation, a gestational sac should be visualized between 4 and 5 weeks gestation and must be present with a beta-HCG greater than 1500–2000 mIU/mL. The yolk sac should be visualized between 5 and 6 weeks gestation and must be present with a gestational sac >10 mm, the embryo should be visualized between 5 and 6 weeks gestation and must be present with a gestational sac >18 mm, and cardiac activity should be visualized between 5 and 6 weeks gestation and must be present if the crown-rump length is greater than 5 mm [3]. The presence of a gestational sac with a diameter greater

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than 20 mm without an identifiable embryo or presence of an embryo with a crown-rump length greater than 5 mm without a heartbeat is diagnostic of a pregnancy demise [4].

In patients with unclear course, serial quantitative beta-HCGs and ultrasounds may be beneficial. Between the 4th and 8th week of gestation, beta-HCG levels should double every 48–72 h. Likewise, both the diameter of the gestational sac and the crown-rump length should increase by 1 mm/day. Therefore, repeating labs and an ultrasound in 7–10 days should demonstrate a measurable change in both.

Prevention

Several interventions can lower the risk of spontaneous abortion. These include avoiding smoking, drinking alcohol, and using recreational drugs. Additionally, avoiding exposure to certain viral infections such as rubella can lower the risk. Finally, obesity increases the risk of miscarriage; therefore, patients should be encouraged to achieve a healthy weight prior to pregnancy.

Management

Miscarriage can be managed expectantly, medically, or surgically. Frequently, spontaneous abortions complete without intervention. In women with significant bleeding, pain, or infection, either medical or surgical intervention should be considered [5]. Other women may desire to avoid the watchful waiting that is often required with expectant management. Misoprostol administered either 600 micrograms orally or 600–800 micrograms vaginally can be utilized for medical management of miscarriage. The initial dose can be repeated in 24–48 h if the initial dose is unsuccessful [6]. Surgical management can be performed using either sharp curettage or vacuum aspiration. While complication rates are comparable between the two, vacuum aspiration is faster and causes less pain and bleeding [7].

Ectopic Pregnancy

Ectopic pregnancy is the implantation of an embryo outside of the uterine cavity. The vast majority are located in the fallopian tubes; however, they may rarely occur in the broad ligament, cervix, ovary, or abdominal cavity. Ectopic pregnancy is the second most common cause of maternal mortality.

Epidemiology

Between 2002 and 2007, a study of women enrolled in health plans demonstrated the ectopic pregnancy rate in the United States to be 0.64% [8]. Previous data, which included patients enrolled in Medicaid, demonstrated a rate of 1.9% in 1992 [9]. Both data sets demonstrate an increasing rate of ectopic pregnancy with age. Mortality rates have declined from 1.15 deaths in 100,000 live births to 0.50 deaths per 100,000 live births between 1980–1984 and 2003–2007 [10]. This is a result of increased awareness and improvements in early diagnosis.

Etiology

Any factor that interferes with the fallopian tube's function and ciliary motility increases the risk of ectopic pregnancy. Risk factors can be divided into anatomic and functional. Anatomic risk factors include a history of tubal ectopic pregnancy, infection (e.g., pelvic inflammatory disease), ligation, or surgery. Functional risk factors include hormonal stimulation of ovulation, use of progestin-containing contraceptives, and tobacco use. Risk factors can also be divided based on the strength of their risk for ectopic pregnancy. Factors strongly associated with ectopic pregnancy include previous ectopic pregnancy, history of tubal surgery, and history of DES exposure. Factors moderately associated with ectopic pregnancy include history of sexually transmitted infection, having more than one sexual partner, and cigarette smoking. Finally, factors slightly associated with ectopic pregnancy include prior

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abdominal or pelvic surgery, douching, and sexual intercourse prior to age 18 [11].

Diagnosis

Most patients presenting with an ectopic pregnancy will have abdominal pain, typically lower abdominal and unilateral, and bleeding. Physical examination may help identify a tender adnexal mass, as well as signs of shock (hypotension, tachycardia, altered mental state) or hemoperitoneum (distended abdomen with decreased bowel sounds, referred shoulder pain, and a posterior cul-de-sac which bulges into the vaginal fornix). Serum hCG and progesterone can both contribute to making the diagnosis of anectopic pregnancy. Serum hCG will typically increase early in pregnancy then plateau and possibly fall. If the initial hCG is <1500 mIU/mL, a rise of at least 53% over 48 h is indicative of a viable pregnancy [12].

A recent meta-analysis reviewing 26 cohort studies, including over 9400 women in the first trimester of pregnancy, found that in women with abdominal pain and/or bleeding and an inconclusive ultrasound, a single progesterone test (cutoff between 3.2 and 6 ng/mL) predicts a nonviable pregnancy with pooled sensitivity of 74.6% (95% confidence interval 50.6–89.4%) and specificity of 98.4% (90.9–99.7%) [13].

The gold standard for diagnosis of ectopic pregnancy is the transvaginal ultrasound. At an hCG level between 1500 and 2000 mIU/mL or higher, a gestational sac should be seen in the uterus using transvaginal ultrasound. Identification of an intrauterine pregnancy essentially rules out ectopic pregnancy (heterotopic pregnancy is exceedingly rare). Ectopic pregnancy is very likely if any adnexal mass or significant free pelvic fluid is identified. Finally, ectopic pregnancy is confirmed if a gestational sac with embryo and heartbeat is identified outside of the uterus [14].

Prevention

While there is no specific prevention strategy for ectopic pregnancy, the risk can be minimized by avoiding modifiable risk factors that increase the risk of an ectopic. These include not smoking, avoiding pregnancy before age 18, and taking precautions to prevent sexually transmitted infections.

Management

The management of ectopic pregnancy can be expectant, medical, or surgical. In reliable patients with an hCG <1000 mIU/mL that is declining, expectant management can be considered if there is minimal pain and bleeding and no evidence of rupture, and if a mass is detected, it is <3 cm in diameter, and no fetal heartbeat is detected [15]. Close follow-up is required, and hCG levels should be followed until they are <5 mIU/mL.

Medical management of ectopic pregnancy has utilized the folic acid antagonist, methotrexate. Single-dose methotrexate is administered at 1 mg/kg or 50 mg/m^2. It should be considered in patients with stable vital signs, an hCG of <2000 mIU/mL, a mass < = 3.5 cm in diameter without fetal heartbeat, and no evidence of rupture. Additionally, patients should not have a contraindication to methotrexate administration such as elevated liver enzymes, immunodeficiency, or blood dyscrasias. Serum hCG levels should be checked at days 4 and 7 and then weekly until it is <5 mIU/mL. If the hCG level does not fall between days 4 and 7, a second dose of methotrexate or surgical intervention should be considered [16, 17].

Surgical management of ectopic pregnancy should be considered when the patient is unreliable for follow-up, is unstable, has signs of hemoperitoneum, or has a more advanced ectopic pregnancy. Additionally, surgical intervention should be considered when the diagnosis is unclear or there is a contraindication to either expectant or medical management. Surgical interventions include linear salpingostomy (opening the fallopian tube and removing the ectopic pregnancy) or salpingectomy (removing the fallopian tube) via laparoscopy or laparotomy. Salpingostomy is preferred in patients who wish to maintain fertility [18]. Laparotomy should be limited to patients in whom visualization is

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compromised or hemostasis cannot be achieved utilizing laparoscopy [19].

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy can be classified into chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia. The term "gestational hypertension" replaces "pregnancy-induced hypertension." The nomenclature of "mild" and "severe" preeclampsia has been abandoned, and preeclampsia is now characterized as being with or without severe features [20]. This distinction helps to emphasize that severe features may develop at any time and that ongoing evaluation is essential in identifying patients with more severe disease.

Epidemiology

Hypertensive disorders of pregnancy affect between 6% and 8% of pregnancies in the United States making them the most common medical complication of pregnancy [21]. The majority of women that develop preeclampsia are nulliparous. In multiparous women, those with multiple gestations, age > 40, history of preeclampsia in prior pregnancy, chronic disease (hypertension, diabetes, and renal disease), elevated BMI, and the presence of the antiphospholipid syndrome increase the risk of developing preeclampsia [22]. Approximately 20% of women with chronic hypertension will develop preeclampsia [20]. Additionally, a family history of preeclampsia, African-American and Latina race, lower socioeconomic class, and women who do not seek or do not have access to prenatal care are at increased risk for developing preeclampsia [20].

Etiology

It has been hypothesized that the pathophysiology of preeclampsia may be the result of a genetic predisposition, an immunologic condition, abnormal implantation of the placenta, endothelial injury to the vascular system, activation of platelets, placental growth factor deficiency, or vasoconstriction as a result of maladaptation of the cardiovascular system. Despite these theories, the exact etiology remains unknown [23].

Diagnosis

Hypertension during pregnancy is defined as a blood pressure of > = 140/90 on two separate occasions 4 h apart or > = 160/110 on a single occasion. Chronic hypertension is defined as hypertension that presents before 20 weeks of gestation or that persists after 6 weeks postpartum. Gestational hypertension is ultimately a provisional diagnosis. It is defined as the presence of hypertension after 20 weeks gestation without the features of preeclampsia defined below. Of those women initially diagnosed with gestational hypertension, approximately 50% will go on to develop preeclampsia [24]. Another proportion will have persistent hypertension after 6 weeks postpartum and be diagnosed with chronic hypertension.

In preeclampsia, hypertension (blood pressure > = 140.90) develops after 20 weeks of gestation and is accompanied by proteinuria. Proteinuria can be identified through a 24 h protein demonstrating > = 300 mg of protein, a protein/creatinine ratio of >0.3 on a random voided urine, or a dipstick of +1 protein on a random voided urine. It is important to note that the presence of edema is no longer a criterion for preeclampsia [20].

Severe features of preeclampsia include two blood pressures of > = 160/110 obtained 4 h apart while the patient is on bed rest, a platelet count <100,000/mL, doubling of AST or ALT, severe right upper quadrant pain without other etiology, creatinine >1.1 mg/dL, doubling of baseline creatinine without evidence of other renal disease, development of pulmonary edema, and cerebral/visual disturbances that did not preexist. Intrauterine growth restriction and proteinuria >5 g in a 24 h urine collection are no longer considered criteria for severe features [20].

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Prevention

A Cochrane review of prophylactically treating women with increased risk of developing preeclampsia with low-dose aspirin demonstrated that the numbers needed to treat to prevent one case of preeclampsia and one fetal death were 69 and 227, respectively [25]. Among women with the highest risk of developing preeclampsia, the number needed to treat to prevent one case of preeclampsia was 18 [25]. Similarly, a Cochrane review of calcium supplementation demonstrated reduced risk of preeclampsia among women at high risk for this condition with low calcium intake [26]. However, routine prophylaxis/supplementation with calcium, magnesium, omega 3 fatty acids, vitamin C, and vitamin E in low-risk patients has not been demonstrated to be effective in lowering the risk of preeclampsia.

Management

For both gestational hypertension and preeclampsia without severe features, patients should be instructed to do daily kick counts to assess for fetal well-being and to self-assess for severe signs or symptoms such as development of a new headache, visual disturbances, chest pain, shortness of breath, persistent nausea and vomiting, or right upper quadrant pain. Patients should be evaluated in the office weekly with blood pressure measurement, platelet count, and liver enzymes. For patients with gestational hypertension, urine should be collected weekly to assess for protein. There is low-quality evidence to support weekly antenatal testing. Additionally, serial ultrasounds should be obtained to assess for growth restriction. Bed rest is no longer recommended [20]. In both gestational hypertension and preeclampsia without severe features, delivery is recommended at 37 weeks gestation [20]. Neither magnesium sulfate during labor nor antihypertensives are recommended.

Once a patient develops preeclampsia with severe features > = 34 weeks gestation, the goal is to stabilize the patient and move toward delivery. If the patient is <= 34 weeks gestation, they should be cared for at a facility that has the required resources to provide care to both the mother and premature fetus. For women who develop preeclampsia with severe features before fetal viability is attained (22–24 weeks depending on location and available resources), once the patient is stabilized delivery should be planned. In women with preeclampsia and severe features <= 34 weeks gestation who are stable, expectant management with close monitoring and appropriate hypertensive control is recommended until the patient is >34 weeks gestation, and then delivery should be planned. In women with preeclampsia with severe features who have reached viability but are <34 weeks gestation and also present with preterm premature rupture of membranes, labor, platelet count <100,000/mL, AST or ALT elevated > twice the upper limit of normal, growth restriction, severe oligohydramnios, new onset or worsening renal dysfunction, or reversed end-flow umbilical Doppler readings, steroids should be administered to promote fetal lung maturity, and an attempt should be made to delay delivery for 48 h to maximize their effectiveness. For patients <34 weeks who present with preeclampsia with severe features and uncontrollable severe hypertension, eclampsia, pulmonary edema, placenta abruption, disseminated intravascular coagulopathy, or Category III fetal heart rate tracing (defined as a sinusoidal pattern or a tracing with absent variability and recurrent late decelerations, variable decelerations, or bradycardia, replaces "non-reassuring" terminology), steroids should be administered to promote fetal lung maturity, but delivery should not be delayed to maximize effectiveness of the steroids. Finally, in women with intrauterine fetal demise, steroid administration is unnecessary, and delivery should be planned [20].

Magnesium sulfate is recommended for patients who present with either preeclampsia with severe features to prevent a seizure or eclampsia to prevent further seizures. The Magpie Trial determined that in women with severe preeclampsia (old nomenclature), 63 women

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needed to be treated with magnesium sulfate to prevent one seizure [27]. Magnesium sulfate should typically be continued until 24 h postpartum or until the patient has demonstrated significant diuresis indicating resolution of vasoconstriction.

Antihypertensive medications are indicated in patients that have blood pressures > = 160/110, although the optimal blood pressure goal is unclear. In acute management, intravenous medications offer a rapid onset and the ability to titrate therapy. Both labetalol and hydralazine have been commonly used. For chronic management of patients with preeclampsia with severe features being expectantly managed, oral medications are preferred. Both oral nifedipine and labetalol have been used in these patients [21].

Placenta Previa

Normal placental implantation occurs at the uterine fundus. Placenta previa, however, occurs when the site of implantation is the lower uterine segment and the placenta overlies or approaches the cervical os. Marginal previa is defined as placenta located within 2 centimeters of the os, whereas complete previa indicates that the placenta covers the os. Morbidity related to placenta previa occurs with maternal hemorrhage, need for cesarean delivery, and risk of abnormal placental implantation (accreta, increta, percreta) which may result in hysterectomy.

Epidemiology

Placenta previa affects approximately 0.4% of pregnancies at term [28]. It typically presents as painless vaginal bleeding in the second or third trimesters which are often triggered by sexual intercourse. Risk factors include chronic hypertension, history of uterine curettage or cesarean delivery (incidence increases to 2.3% after just two cesarean deliveries [29]), cocaine or tobacco use, increasing maternal age, multiparity, and male fetuses [28].

Etiology

The exact etiology of placenta previa is unknown. It has been hypothesized that atrophy or scarring of the endometrium related to prior trauma, surgery (uterine curettage or cesarean), or infection may lead to inadequate or abnormal vascularization of the endometrium in the fundus to allow for implantation [30]. Further research is required to evaluate this hypothesis.

Diagnosis

The diagnosis of placenta previa should be suspected in women who present in either the second or third trimester with painless vaginal bleeding. Additionally, persistent breech or malpresentation at term should raise suspicion. Diagnosis is confirmed with ultrasonography to locate the site of placental implantation. Transvaginal ultrasound is more sensitive and specific than transabdominal ultrasound and has been demonstrated to be safe to perform [31]. In patients in whom abnormal insertion is suspected (accreta, increta, percreta), MRI may be useful in differentiating the level of invasion into the uterine wall.

Prevention

While there is no specific prevention strategy for placenta previa, the risk can be minimized by avoiding modifiable risk factors that increase risk for previa. These include not smoking or using cocaine when considering and during pregnancy and careful consideration of first cesarean in patients who desire additional children.

Management

The management of placenta previa remains somewhat controversial. Most authors recommend expectant management between the time

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of identification of previa and the first (sentinel) bleed as long as they have ready access to a hospital that provides maternity care services [32]. A similar strategy is reasonable for patients after a sentinel bleed following a period of inpatient hospitalization, stabilization, and observation. Patients should be advised to avoid placing any object in the vagina, including intercourse and tampons. In patients with recurrent bleeding, delivery should be considered at 36 weeks gestational age; and in patients without vaginal bleeding, delivery should be considered at 38 weeks gestational age [32].

In women with marginal previa, the mode of delivery should be determined following ultrasound at 36 weeks. If the placental edge is $> =$ 2 cm from the cervical os, an attempt of vaginal delivery should be made. In cases where the placental edge is 1–2 cm from the cervical os, vaginal delivery can be considered; however, facilities should be prepared for the need for emergent cesarean delivery [33].

In women with complete previa, cesarean delivery should be planned for between 36 and 38 weeks gestation, as noted above. Because of the increased risk of placenta accreta, increta, or percreta, the delivery team should be prepared to perform a cesarean hysterectomy [32].

In women with recurrent episodes of bleeding prior to delivery, transfusion should be considered for signs or symptoms of symptomatic anemia. Additionally, because of the risk of severe postpartum hemorrhage and disseminated intravascular coagulopathy during or following delivery, patients should be evaluated for transfusion and the blood bank notified of the potential need to activate massive transfusion protocols.

Preterm Labor and Delivery

Preterm labor is defined as the development of regular uterine contractions that result in cervical change, effacement, and dilation, occurring before 37 weeks of gestation. The greatest risk of preterm labor is resultant preterm delivery.

Epidemiology

In the United States, 11.39% of deliveries in 2013 occurred prior to 37 weeks [34], 40–45% of which are the result of preterm labor without premature rupture of membranes [35]. Between 1990 and 2006, the incidence of preterm delivery increased 20%, largely as a result of an increase in multiple gestations (resulting from increased use of assistive reproductive technology) and late preterm deliveries. Since that time, with an increased focus on decreasing the number of near-term inductions and cesarean deliveries, that rate has fallen to a 15-year low [34, 35]. While efforts persist to decrease the number of preterm deliveries, it will be difficult to eliminate them completely as 30–35% of preterm deliveries are secondary to medically indicated inductions or cesarean deliveries (preeclampsia with severe features, placental abruption, etc.) [35].

Etiology

Common pathways resulting in preterm labor and delivery include immune mediation, inflammation, stress, overdistension of the uterus, uteroplacental hemorrhage, and uteroplacental ischemia [36]. Many risk factors for preterm labor and delivery, which activate these pathways, have been identified and can be divided into preconception, maternal, and fetal factors. These are summarized in Table 1. Unfortunately, nearly 50% of preterm deliveries occur in women without known risk factors for preterm labor or delivery [37]. Of the known risk factors, history of both spontaneous and medically indicated preterm delivery is the most significant distinguishable risk factor for recurrence, increasing the risk by 2.5-fold [38].

Infection is an important cause of preterm labor and delivery and may be responsible for 25–40% of all preterm births. Bacterial vaginosis increases the risk of preterm delivery between 1.5 and 3 times. In women with the TNF-alpha allele 2 gene, the presence of bacterial vaginosis doubles the risk of preterm delivery [36]. Asymptomatic bacteriuria and pyelonephritis have both been

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Table 1 Risk factors for preterm delivery

Preconception	Maternal	Fetal
Body mass index <20 or poor nutrition	Abdominal surgery	Assisted reproductive technology (both singleton and multiple Gestations)
History of LEEP or cone biopsy of the cervix	African-American race	Congenital anomalies
Interpregnancy interval <6 months	Chronic medical conditions (diabetes, Hypertension)	Intrauterine fetal demise
Psychological stress and emotional or Physical abuse	History of preterm delivery	Intrauterine growth restriction
Sexually transmitted illnesses	Infection (bacterial vaginosis, chlamydia, Trichomonas)	Multiple gestation
Smoking	Lack of prenatal care	
Substance abuse (cocaine, amphetamines)	Oligohydramnios	
Uterine anomaly	Periodontal disease	
	Placenta abruption	
	Placenta previa	
	Polyhydramnios	
	Poor social support	
	Short cervix	
	Smoking	
	Strenuous work	
	Uterine contractions	

associated with preterm delivery. Periodontal disease increases the risk by twofold. Sexually transmitted infections including chlamydia, gonorrhea, and syphilis likewise increase the risk of preterm birth. While group B *Streptococcus*, *M. hominis*, and *U. urealyticum* are commonly identified in women with preterm labor, they are not felt to be causal of the preterm labor [35].

Diagnosis

Patients presenting with complaint of preterm contractions should be placed on a tocodynamometer to assess for frequency of uterine contractions. Fetal well-being should be assessed by continuous Doppler and position determined by ultrasound.

In a patient presenting with preterm contractions, assessment should evaluate for status of amniotic membranes (intact or ruptured), presence of infection, and likelihood that contractions will lead to delivery. Evaluation for rupture of membranes is discussed below in the section entitled "Premature Rupture of Membranes." Patients should be evaluated for bacterial vaginosis, gonorrhea and chlamydia, urinary tract infection, and group B *Streptococcus*.

Likelihood of delivery can be assessed via digital cervical examination, terbutaline challenge, fetal fibronectin collection, and measurement of cervical length. Digital cervical examination, while subjective in nature, may be useful if advanced dilation or effacement is noted on examination. A single dose of terbutaline 0.25 mg administered subcutaneously may result in resolution of contractions in patients not in preterm labor. Fetal fibronectin, a placental glycoprotein, is typically absent from vaginal secretions prior to term, and its presence between 24 and

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34 weeks has been associated with preterm delivery. The presence of fetal fibronectin in vaginal secretions collected in the posterior fornix between 24 and 34 weeks has a positive predictive value of 13–30% for delivery in the next 7–10 days. Its absence has a negative predictive value of 99% for delivery in the following 2 weeks [39]. False-positive results may occur if the patient has had intercourse, a digital cervical exam, or transvaginal ultrasound in the past 24 h or is having active bleeding from the cervix or vagina. Transvaginal measurement of cervical length can also be useful in stratifying risk for preterm delivery. In symptomatic women, an initial cervical length of >30 mm excludes the diagnosis of preterm labor, whereas women with a cervical length < 15 mm are at high risk for preterm delivery [40].

Prevention

In women with a history of preterm delivery (spontaneous and not medically indicated), 17-alpha-hydroxyprogesterone caproate (17P) has been demonstrated to reduce the recurrence rate of preterm delivery. It is indicated in women between 16 and 36 weeks gestation who have a history of preterm delivery, who have not demonstrated signs of preterm labor in the current pregnancy, and who are not allergic to the compound. Beginning at 16 weeks, patients should receive 250 mg intramuscularly weekly through 36 weeks or delivery. Studies have demonstrated a decrease in preterm deliveries in women meeting the above criteria who are treated with 17P versus controls (37% vice 55%) as well as an improvement in the health of their infants [41]. Vaginal progesterone has not been shown to be beneficial in this population.

Women with a history of preterm delivery should have their cervical length evaluated by transvaginal ultrasound between 16 and 24 weeks gestation [42]. If the cervical length is found to be <25 mm, cervical cerclage should be offered. Studies have demonstrated a decrease in preterm birth and perinatal morbidity and mortality when cerclage is used in this population [42]. Additionally, in women with history of preterm delivery and a cervical length of <20 mm, vaginal progesterone 100–200 mg administered vaginally on a daily basis has shown to decrease rates of preterm delivery and perinatal morbidity and mortality [43]. Intramuscular progesterone has not been demonstrated to improve outcome in this population.

It is important to note that while published meta-analyses have reported the benefits above with the use of either intramuscular or vaginal progesterone, three recent trials (OPPTIMUM, PROGRESS, and PROLONG) failed to demonstrate similar decreases in preterm labor rates and/or fetal death [44, 45, 46]. As a result, while progesterone remains widely utilized, there is some controversy, in particular for the use of intramuscular progesterone.

Although several studies have examined the treatment of asymptomatic bacterial vaginosis in the prevention of preterm labor and delivery, data remains conflicted. The US Preventive Services Task Force recommends against screening in low-risk women and states that there is insufficient evidence to recommend for or against screening and treatment of women at high risk for preterm labor [47].

Management

Women diagnosed with preterm labor should, when feasible, be transferred to a facility that has the capability to manage a preterm infant. Antenatal corticosteroids should be administered to women between 24 and 34 weeks gestation who present in preterm labor. Either betamethasone 12 mg administered intramuscularly for two doses 12 h apart or dexamethasone 6 mg administered intramuscularly for four doses 6 h apart has been shown to be effective in decreasing perinatal morbidity and mortality [48]. Magnesium sulfate administered intravenously as a 4–6 g bolus followed by a maintenance dose of 1–2 g/h for 24 h in women with preterm labor has been shown to decrease the

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rate of cerebral palsy in their infants [49]. It should be noted that magnesium sulfate is no longer recommended for use as a tocolytic in these patients.

Short-term tocolysis may be considered in women presenting with preterm labor to allow time to transfer to a facility with a higher level of.

care, to allow administration of corticosteroids and magnesium sulfate, and to provide for group B *Streptococcus* prophylaxis. Nifedipine has been shown to decrease the risk of delivery within 48 h and has the advantage of increased latency till birth, improved neonatal outcomes, and decreased maternal side effects compared to other tocolytics [48]. Beta mimetics, such as terbutaline, may also be used to delay delivery. Magnesium sulfate, on the other hand, has not been shown to prolong pregnancy or to improve perinatal morbidity [50].

Group B *Streptococcus* is the leading cause of death secondary to infection in newborns despite widespread implementation of CDC guidelines for its prevention. In women presenting with preterm labor, either ampicillin 2 g intravenously on admission then 1 g every 4 h through delivery or penicillin G 5 million units intravenously on admission then 2.5–3 million units every 4 h through delivery should be administered [51]. Dosing may be discontinued if preterm labor is ruled out or if a negative group B *Streptococcus* culture is obtained. Cefazolin should be used in women with a non-anaphylactic allergy to penicillin. In women with a history of anaphylaxis, clindamycin or vancomycin should be utilized.

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Problems During Labor and Delivery 13

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Introduction

Labor is a process, and difficulties can arise at any point. This chapter will outline antepartum considerations and focus on the complications that can arise as labor progresses. It is important to keep in mind, however, that there is much overlap in the timing of these questions and problems. The clinician must try to anticipate them early.

Trial of Labor and Vaginal Birth After Cesarean Section

Background

Trial of labor after cesarean delivery (TOLAC) refers to a planned attempt at vaginal delivery by a woman who has previously undergone a cesarean delivery. It is well known that the cesarean section rate has dramatically increased over several decades. Supported by accumulating evidence of relative safety, increased offering of TOLAC represented a countertrend from the 1970s to 1990s, with a resultant decrease in the cesarean rate [1]. However, as more reports of complications such as uterine rupture surfaced, this trend reversed. Among other interested parties, the National Institutes of Health (NIH) in 2010 called on organizations to facilitate access to TOLAC, in an effort to improve perinatal outcomes by reducing complications associated with repeat cesarean sections [1].

Uterine Rupture

The most feared complication of TOLAC is uterine rupture, which can result in significant maternal and fetal morbidity and mortality. Uterine rupture usually involves the previous hysterotomy scar but may extend into the uterine wall or

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beyond. Risk factors include excessive oxytocin administration, dysfunctional labor, history of more than one cesarean, multiparity, short interdelivery interval, and history of nonpregnant uterine perforation [1]. Rates of rupture are difficult to estimate due to a paucity of data, but available literature suggests rates of 4–9% after a classical incision, 0.5–0.9% after a low transverse incision [1], and 1–4% after a low vertical incision [2]. Uterine rupture most frequently presents with fetal heart rate abnormalities. Other symptoms and signs may include abdominal pain, decrease in frequency and/or intensity of contractions, bleeding, or loss of fetal station. Emergent laparotomy may be indicated for any of these findings, as fetal death or adverse neurologic outcomes may occur in as many as 25% of cases of uterine rupture [3].

Approach to the Patient

Decreasing the occurrence of repeat cesareans would be an obvious benefit due to lower rates of hemorrhage, thromboembolism, infection, and surgical complications, as well as a shorter recovery period. However, the endeavor to compare elective repeat cesarean (ERC) with a trial of labor (TOL) in patients with a history of one prior cesarean is complex. The decision of whether to undergo a TOL involves assessing both the chance of successful vaginal birth after cesarean (VBAC) and the risks associated with TOLAC. The calculator most commonly used to stratify this risk is available on the website for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network (https://mfmunetwork.bsc.gwu.edu/PublicBSC/MFMU/VGBirthCalc/vagbirth.html). Probability for successful VBAC is based on a multivariable logistic regression model which allows for more individualized counseling of pregnant patients with a prior cesarean. It should be noted that while race is a factor in the current calculator, its role is unclear and a model that does not include race or ethnicity is under development.

The decision regarding mode of delivery is ultimately patient-specific, reached after conversation with her provider beginning early in pregnancy. Although there is no consensus, it has been suggested that patients with at least a 60–70% predicted chance of successful VBAC do not have an increased likelihood of morbidity when compared to patients undergoing ERC [1].

Management

The most recent ACOG Practice Bulletin on this issue made a number of recommendations based on "good and consistent scientific evidence" [1]: most patients with one prior low transverse cesarean section should be offered TOLAC; epidural analgesia may be used in patients undergoing TOLAC; misoprostol should not be used for cervical ripening or induction of labor. A number of recommendations were made based on more limited scientific evidence, including that TOLAC is a reasonable option for patients with two prior cesarean deliveries, as well as for patients with an unknown type of uterine scar as long as there is no high clinical suspicion for a classical uterine incision. The bulletin also notes that induction of labor remains an option, although it is critical to recognize that prostaglandin and oxytocin use are key risk factors for complete uterine rupture in both intact and scarred uteri [1, 43]. ACOG recommends a trial of labor even for patients with twins and a history of one low transverse cesarean delivery, as long as the first twin is cephalic [1].

Indications for Cesarean Delivery

Cesarean delivery was once considered the last resort, resulting in maternal death in the majority of cases [4]. It is now generally viewed as safe and increasingly requested and performed without clear indication. It is imperative to understand appropriate indications for cesarean section.

Four indications currently account for up to 90% of cesarean sections: prior cesarean section (~35–40%), labor dystocia (~20–35%), abnormal fetal presentation (~10–20%), and non-reassuring fetal status (~10–25%) [4, 5]. See Table 1 for a helpful categorization of cesarean indications, suggested in *Munro Kerr's Operative Obstetrics*

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Table 1 Indications for cesarean section

Indisputable	Generally accepted[a]	Marginal
Placenta previa	Previous cesarean section	Fear of repeating previous bad outcome
Confirmed fetal compromise or imminent fetal demise (*clear fetal heart rate evidence, umbilical cord prolapse, vasa previa, uterine rupture, severe placenta abruption*)	Breech presentation	Fear of fetal injury
Definite obstruction (*unequivocal cephalopelvic disproportion, soft tissue obstruction, fetal malpresentation*)	Labor dystocia	Fear of maternal pelvic floor injury
	Concern for fetal compromise	
	Maternal medical conditions *(severe preeclampsia, severe cardiovascular disease, super obesity)*	

[a]Within this category, indications may range from relative to absolute

[4]. Frequently, a combination of relative indications, rather than one absolute indication, leads to the decision for cesarean.

Breech Delivery

Background

The Term Breech Trial in 2000 led to a dramatic change in obstetric practice [6]. When compared with planned cesarean delivery, the study demonstrated increased morbidity with planned vaginal breech delivery. Follow-up analyses have suggested short-term benefits in both maternal and neonatal morbidity and mortality from planned cesarean delivery, but the evidence is not yet clear on the persistence of long-term risk for mother or infant [7]. Hesitance to plan vaginal breech deliveries has persisted, and consequently, practitioner experience and comfort with performing this procedure has decreased [8]. ACOG expresses support for shared decision-making between the patient and practitioner that considers both patient wishes and practitioner experience. They note that planned vaginal breech delivery "may be reasonable under hospital-specific guidelines for eligibility and labor management" [8], but only after detailed informed consent that explicitly documents that the risk for neonatal morbidity and mortality may be higher than if a cesarean delivery is planned. Additionally, ACOG recommends first offering external cephalic version as an alternative to cesarean delivery for women desiring vaginal delivery who carry a term singleton breech fetus and have no other contraindications [8].

General Principles

Breech presentation persists in approximately 3–4% of singleton pregnancies at term [5]. There are several types of breech presentation, defined by the relationship of the lower extremities to the buttocks. In frank breech presentation, the hips are flexed and the knees extended, so that the feet are close to the head. In complete breech presentation, one or both of the knees are flexed. In incomplete breech presentation (also referred to as footling breech), one or both knees are not flexed and therefore below the buttocks. As a pregnancy approaches term, the larger mass of the buttocks typically finds its place in the more spacious fundus. Multiple factors increase the risk of breech presentation [5]: amniotic fluid volume abnormalities, high parity, hydro-/anencephaly, previous breech delivery, uterine anomalies, placenta previa, fundal placentation, and pelvic tumors. Risks of vaginal breech delivery include maternal cervical and vaginal trauma; uterine rupture; fetal humerus, clavicle, or femur injuries; brachial plexus injuries; skull fractures; and difficulty delivering the after coming head.

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Management

Because unexpected breech deliveries occur, and because some resource settings make cesarean section impossible, it is important to understand the technique of breech delivery. While multiple sources describe the technique in detail, several points are worth mentioning: episiotomy should be strongly considered; delivery is easier if the fetus is allowed to deliver spontaneously up to the umbilicus, in order to avoid cord compression; delivery must be accomplished promptly once the breech has passed through the introitus [5].

Bleeding Complications During Labor

General Principles

Patients who have placenta abruption, placenta previa, placenta accreta, and vasa previa can present with vaginal bleeding later in pregnancy. It is important to understand the conditions and respond quickly when there is a high index of suspicion. Advances in ultrasonography have improved the early and accurate diagnosis of placenta previa, placenta accreta, and vasa previa allowing the clinician time for preparation.

Placental Abruption

Placental abruption occurs when there is premature separation, either partial or total, of the placenta from the uterine wall prior to birth. Placental abruption occurs in 0.6–1% of pregnancies [9], and the primary risk factor is hypertension. Other risk factors for placental abruption include abdominal trauma, grand multiparity ($\geq$3), uterine anomalies, folate deficiency, short umbilical cord, cigarette smoking, cocaine use, history of abruption, maternal age over 35, obesity, and use of assisted reproductive technology [9, 10]. Most women will experience third trimester bleeding (80%), acute abdominal pain (50%), and/or a non-reassuring fetal heart rate tracing. Ultrasonography does not always detect a clot underneath the placenta; therefore, placental abruption remains a clinical diagnosis and treatment is recommended if there is a high index of suspicion. Close monitoring of mother and baby is necessary. The mother may become hemodynamically unstable and require IV fluids or blood products. When there is a non-reassuring fetal heart rate tracing, an emergency cesarean section may be necessary.

Placenta Previa

Placenta previa occurs when the placenta overlies or is proximate to the cervical os. Placenta previa can be classified as complete if the placenta completely covers the internal os, partial if the placenta partially covers the internal os, marginal if the placenta reaches the internal os but does not cover it, or low-lying placenta if the placenta extends into the lower uterine segment but does not reach the internal os.

Placenta previa may be seen in up to 1.3% of all births [10, 11]. Risk factors include multiparity, previous placenta previa, history of cesarean section, history of dilation and curettage, smoking, pregnancy termination, prior evacuation of retained products of conception, advanced maternal age, multifetal gestation, abnormal fetal lie, and previous intrauterine surgery. The condition is a relatively common finding, often diagnosed incidentally in asymptomatic women by second trimester ultrasounds. Transvaginal ultrasound is the superior method of detection. Once diagnosed, repeat ultrasonography in the third trimester is indicated. If the placenta previa is marginal, they tend to resolve in 95% of cases. Symptomatic women present during their third trimester with painless vaginal bleeding. Placenta previa is associated with antepartum bleeding, the need for hysterectomy, maternal hemorrhage, blood transfusion, septicemia, thrombophlebitis, and an increased risk of preterm birth [10]. Once diagnosed, the initial management is usually conservative as long as there is a reassuring fetal heart rate tracing and the mother is hemodynamically stable, in order to allow for the fetus to progress to as close to term as possible. If bleeding occurs between 24 and 34 weeks of gestation, it is also

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recommended to administer steroids in case preterm delivery is necessary. Planned cesarean section for complete or partial placenta previa is usually performed at 36–37 weeks of gestation [10].

Placenta Accreta

Placenta accreta refers to a placenta that is abnormally adhered to the uterus, invading the myometrium, serosa, or even adjacent organs. This becomes a problem at the time of delivery when the placenta does not separate and may lead to massive hemorrhage. This hemorrhage can cause further complications such as disseminated intravascular coagulopathy, need for hysterectomy, injury to other maternal tissues, renal failure, or death [10]. The incidence of accreta is rising due to the rise in cesarean delivery rates [10] and is estimated to occur in between one in 533–730 deliveries, an eight-fold increase since the 1970s [12]. In addition to prior cesarean delivery, the other major risk factor for placenta accreta is placenta previa; the risk is greatest when both factors are present and the previa overlies the hysterotomy scar [12]. Additional risk factors include prior uterine surgeries, advanced maternal age, multiparity, and in vitro fertilization. It is critical to make the diagnosis of placenta accreta prenatally via sonography or MRI so that proper planning and delivery can occur. Management of placenta accreta involves a planned preterm cesarean section by 34 weeks gestation followed by total abdominal hysterectomy without an attempt to separate the placenta from the uterus to avoid excessive bleeding. As with all planned preterm deliveries at this gestational age, antenatal steroids should be administered prior to delivery. The clinician should be prepared to manage blood loss since women with placenta accreta typically lose 3000–5000 ml of blood at time of delivery [10].

Vasa Previa

Vasa previa is a rare but life-threatening condition that refers to fetal vessels running through the membranes over the cervix and under the fetal presenting part. It is the result of velamentous insertion of the cord into the membranes instead of the safer placenta. Because this can lead to fetal hemorrhage at the time of membrane rupture, it carries a mortality rate greater than 50% [10]. Vasa previa occurs in 1 in 2500 deliveries [10]. Risk factors include a low-lying placenta, placenta with accessory lobes, multiple pregnancies, and pregnancies from in vitro fertilization [10]. Vasa previa can be seen with ultrasonography but is sometimes diagnosed at rupture of membranes when vaginal bleeding is noted along with fetal distress. The diagnosis is confirmed on visual inspection of the placenta after delivery. For vasa previa that is prenatally diagnosed, administration of corticosteroids is recommended at 30–32 weeks with planned cesarean section between 35 and 36 weeks of gestation. Treatment of vasa previa is immediate cesarean section if found at the time of rupture of membranes.

Premature Rupture of Membranes and Preterm Premature Rupture of Membranes

General Principles

Premature rupture of membranes (PROM) at term is defined as rupture of the chorioamniotic membranes more than an hour prior to the onset of labor at 37 weeks of gestation or later. Preterm premature rupture of membranes (PPROM) is defined as the premature rupture of membranes before 37 weeks of gestation. PROM occurs in 8% of pregnancies and PPROM occurs in 2–3% of all pregnancies [13]. About half of PROM patients deliver within 36 h after expectant management only, while half of PPROM patients deliver within 1 week regardless of obstetric management.

Risk factors for PROM include primiparity, prior PROM, preterm labor, first trimester bleeding, and chlamydia infection. Risk factors for PPROM include prior history of PPROM, intraamniotic infection, second or third trimester

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bleeding, cerclage, shortened cervical length, uterine overdistention, smoking, illicit drug use, low socioeconomic status, BMI <20, maternal pulmonary disease, previous LEEP, and nutritional deficiencies [13]. Group B streptococcus (GBS) status is not a risk factor for PROM or PPROM. Both conditions often occur in the absence of any clearly identified risk factors or etiology.

The risk of intra-amniotic infection and postpartum intrauterine infection increases with the duration of membrane rupture. Clinically evident intra-amniotic infection will occur in 15–35% of PPROM patients, and 15–25% will experience postpartum intrauterine infection [13]. Other obstetric complications include placental abruption (2–5% of PPROM patients [13]), umbilical cord compression during labor, and umbilical cord prolapse. The primary risks to the fetus after PPROM are complications of prematurity. Neonatal infection is associated with intra-amniotic infection and positive maternal GBS status in women with term PROM.

Diagnosis

Women will present with a gush or persistent leakage of fluid in both PROM and PPROM. The clinician should perform a speculum exam to inspect for pooling of fluid and do a visual assessment of cervical effacement and dilation. Due to the increased risk of infection, digital cervical examination should be avoided unless clinically indicated by active labor or imminent delivery [13]. The clinician can also perform a nitrazine test to assess for abnormally basic pH of vaginal secretions indicating presence of amniotic fluid, ferning examination, or a commercially available test for amniotic proteins such as AmniSure or ROM Plus. These latter, newer amniotic protein tests are highly sensitive but not specific; the false positive rate falls between 19% and 30%. The United States Food & Drug Administration (FDA) warns that these tests should only be used in combination with other clinical assessments to diagnose rupture of membranes [13].

Treatment

Women presenting with PROM should be induced if labor does not occur near the time of presentation. This is most often accomplished with IV oxytocin, although misoprostol can also be considered as it is equally effective but with greater risk for chorioamnionitis. In the setting of PROM, antibiotics may reduce intra-amniotic and intrauterine infections; however, it has not been shown to improve neonatal outcomes. Thus, the routine use of antibiotics without confirmed maternal infection should be avoided in term patients [13]. Among PPROM patients, a seven-day course of antibiotics (usually IV ampicillin and erythromycin followed by oral amoxicillin and erythromycin) is used to prolong latency and decrease maternal and neonatal morbidity. GBS prophylaxis should be based on prior culture results if available. The treatment of PPROM is dependent on gestational age and assessment of fetal status.

- PPROM at ≥34 weeks of gestation: Induction of labor is recommended, although expectant management may be "reasonably offered" to those between 34 weeks and 36 and 6/7 weeks gestation [13, Level B evidence]. GBS prophylaxis is based on prior culture results or risk factors. A single course of corticosteroids is recommended for women between 34 and 0/7 and 36 and 6/7 weeks gestation who have not previously received an antenatal dose, as long as delivery is expected in no less than 24 h and no more than 7 days.
- PPROM at 24–33 and 6/7 weeks of gestation: Expectant management until 34 weeks if lung maturity is not proven. Treatment with latency antibiotics, corticosteroids, and intrapartum GBS prophylaxis is recommended. Consider the use of magnesium sulfate for fetal neuroprotection if there is a risk of imminent delivery before 32 weeks of gestation.
- PPROM at <24 weeks of gestation (previable): Counsel regarding risks and benefits; including likely neonatal morbidity and mortality. Compare immediate delivery vs. expectant management. Latency antibiotics may be considered at >20 weeks gestation, and corticosteroids may

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be considered at >23 weeks gestation. No GBS prophylaxis necessary. Monitor for signs of infection.

Postterm Pregnancy

General Principles

Postterm pregnancy refers to a pregnancy that is ≥42 and 0/7 weeks of gestation or ≥294 days from first day of the last menstrual period. Early and accurate dating is critical to the diagnosis. In the United States approximately 28% of pregnancies deliver in the 40th and 41st week and 5–7% delivers at over 42 weeks [14]. One risk factor for postterm pregnancy is inaccurate dating. When compared to dating based on LMP, early sonographic dating has been linked to a reduction in prevalence of postterm pregnancy from 6–12% to 2% [15]. Membrane sweeping also decreases the risk of late term and postterm pregnancy [14].

Of the true postterm pregnancies, most have no known etiology. Women at highest risk for postterm pregnancy are those with a previous postterm pregnancy, as the risk is two to three times higher after one prior postterm pregnancy and four times higher after two prior postterm pregnancies [16]. Other risk factors for postterm pregnancy include nulliparity, male fetus, maternal obesity, advanced maternal age, and certain fetal disorders such as anencephaly [14].

Postterm fetuses tend to be larger than term fetuses with a twofold increased risk for macrosomia. This further increases the risk of prolonged labor, shoulder dystocia, meconium-stained amniotic fluid, and cephalopelvic disproportion. These complications increase the risk of birth injury, as well as other sequelae such as failed induction, third or fourth degree lacerations, postpartum hemorrhage, operative delivery, and cesarean section. A postterm pregnancy can also be a cause of emotional distress to the mother. Although the absolute risk of stillbirth remains low, neonatal mortality does increase as the gestational advances beyond 41 weeks, carrying a nearly threefold increased risk of neonatal death between by 43 weeks gestation compared with a 40 week gestation [14]. Other risks to the fetus include neonatal convulsions, meconium aspiration syndrome, low umbilical artery pH, 5-min Apgars less than four, increased rate of NICU admission, and oligohydramnios [14].

Management

In well-dated postterm pregnancies, it is recommended to induce after 42 weeks of gestation regardless of cervical status in order to mitigate perinatal morbidity and mortality [17]. Induction of labor at 41 weeks gestation should be considered and is widely performed. This approach has not resulted in an increased risk of cesarean delivery compared to expectant management. Cervical ripening agents can be utilized in women with unfavorable cervices. The efficacy of antenatal fetal assessment has not been well studied due to ethical implications of assigning patients to the control group. Based on case-control studies, it is reasonable to perform antenatal fetal assessments twice a week beginning at 41 weeks of gestation and these assessment may include nonstress testing, biophysical profile (BPP), or modified BPP (nonstress test plus amniotic fluid volume).

Labor Dystocia

General Principles

The word dystocia means difficult labor [5]. Numerous maternal and fetal complications can result in increased rates of uterine rupture, intrauterine infection, uterine atony following delivery, pathological retraction rings, fistula formation, pelvic floor injury, maternal lower extremity nerve injury, fetal sepsis, and fetal mechanical injuries. Labor dystocia is the most common indication for primary cesarean delivery [18], as well as the underlying factor in at least one-third of all cesarean deliveries [2, 19], and therefore a significant public health concern. The problem is significantly more common in nulliparas than multiparas. Consequently,

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decreasing the incidence of dystocia in nulliparous patients would significantly impact the overall cesarean birth rate [2].

Approach to the Patient

Dystocia has multiple causes, though identifying a specific cause is limited by frequent overlap and lack of definitive diagnostic tools. A common helpful framework divides these causes into problems with *power* (or uterine action), *passenger* (or fetal position in relationship to the maternal pelvis), or *passageway* (or shape and size of the maternal pelvis, i.e., cephalopelvic disproportion). Ineffective uterine action is the most common cause [2, 5], of which there can be various mechanisms (e.g., insufficient strength, incoordination, other events in labor such as [arguably] chorioamnionitis). True cephalopelvic disproportion is likely rare [5] and in practice is diagnosed if labor does not progress normally in the setting of adequate uterine contractions and cephalic presentation. Conceptualizing abnormal labor in this way organizes clinical thought processes and guides interventions.

Diagnosis

No universal set of diagnostic criteria for labor dystocia exists. The labor curves put forth by Friedman in the mid-1900s are increasingly questioned [5], with more recent data suggesting that labor may last longer overall, that the latent phase in particular may last longer, and that labor progress may accelerate as it advances. At the very least, experience since Friedman suggests that labor patterns are contingent on multiple patient variables, including parity, use of regional anesthesia, and fetal presentation [20].

Requiring specific periods of time to pass before diagnosis may not be helpful for each individual labor, but certain conditions should be fulfilled in order to prevent premature decisions [5]. First, dystocia should be diagnosed only after a patient has entered the active phase of labor. Second, every effort should be made to ensure that the patient has been given an adequate trial of labor, which includes adequate contractions over an extended period of time (e.g., 200 Montevideo units per 10 min over 2–4 h). Third, amniotomy should be performed prior to diagnosis [2].

Management/Prevention

The management of labor dystocia follows from the above discussion. As a means of prevention, elective induction should be undertaken with caution. When active labor has been diagnosed, steps should be taken to ensure the adequacy of contractions. Adequacy is determined by Montevideo units, which are most accurately measured by an intrauterine pressure catheter. Especially in the case of nulliparous patients, enhancing the adequacy of contractions will often be accomplished with the use of oxytocin, which is very safe in this group of patients.

Various labor management protocols have arisen since the 1980s, all with the goal of reducing rates of labor dystocia and thereby reducing rates of cesarean delivery. These efforts target nulliparous patients, since rates of dystocia are highest in this group. One such program arose in a large maternity center in Dublin in the 1980s, employing an approach that has come to be known as the "active management of labor" [21]. The protocol achieved remarkable success – one highlight being a low cesarean delivery rate of 4.8%. The overarching lesson from this protocol and others is that the clinician must be vigilant in recognizing and addressing abnormal labor, and then effectively intervene to improve uterine action when necessary.

Infection

Group B Streptococcal Disease

Background

The 1970s witnessed the emergence of group B streptococcus (GBS) as the leading cause of neonatal morbidity and mortality, with reported case-

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fatality rates as high as 50% [22]. Among the 10–30% of mothers colonized with GBS, approximately 50% will transmit the bacteria to their newborn [23]. Guidelines issued in 1996 and 1997 recommended intrapartum antibiotic prophylaxis to prevent neonatal GBS disease [22]. This was followed by guidelines in 2002 recommending universal culture-based screening for GBS colonization in pregnant patients at 35–37 weeks of gestation [22]. These efforts have led to an 80% reduction in the incidence of early-onset neonatal sepsis due to GBS. In 2019, ACOG updated their antepartum screening recommendation, reporting that women from 36 to 37 and 6/7 weeks gestation should undergo screening; patients between 35 and 36 weeks are no longer included. This is to maximize the five-week window of valid culture results to include a gestational age up to 41 weeks. Despite the significant progress in mitigating the risk of neonatal infection, GBS remains the leading cause of neonatal infectious morbidity and mortality [23].

Management/Prevention

Prevention of perinatal GBS disease focuses on early-onset neonatal disease (within the first week of life), as the above efforts have not changed the incidence of late-onset disease [22]. The recommendations for intrapartum management discussed below come from the ACOG Committee Opinion, most recently revised in February 2020 [23].

Intrapartum GBS prophylaxis is always indicated in patients who have had a previous infant with invasive GBS disease, in patients with GBS bacteriuria during the current pregnancy, and in patients with a positive GBS vaginal/rectal culture obtained late in the current pregnancy. In patients whose GBS status is unknown at the time of labor, antibiotic prophylaxis is indicated only in patients with a gestational age less than 37 weeks, rupture of membranes for greater than 18 h, intrapartum fever, or history of GBS positive status in a prior pregnancy. Of note, antibiotic prophylaxis is not indicated for patients with intact membranes undergoing cesarean delivery before the onset of labor, regardless of GBS colonization status. All patients with preterm labor or preterm premature rupture of membranes (PPROM) should be screened for GBS colonization at the time of diagnosis and then treated with appropriate antibiotics for GBS prevention until labor is either ruled out or completed. Ideally, antibiotics should be initiated at least 4 h prior to delivery, though this goal should never delay medically necessary interventions during labor. Penicillin remains the antibiotic of choice, except in the case of severe penicillin allergy in which case cefazolin, clindamycin, or vancomycin would be considered.

Intra-amniotic Infection

General Principles

Intra-amniotic infection (IAI), previously termed "chorioamnionitis," is acute infection and resultant inflammation of one or more of the following: amniotic fluid, placenta, fetus, fetal membranes, or decidua [49]. Most commonly, IAI is caused by polymicrobial bacterial infection ascending from the lower genital tract. IAI complicated 2–5% of pregnancies [24], and may account for half of deliveries prior to 30 weeks and up to 40% of cases of early neonatal sepsis and pneumonia [25].

Risk factors for IAI include prolonged labor, nulliparity, meconium-stained amniotic fluid, longer duration of internal uterine monitoring, the presence of genital tract pathogens such as bacterial vaginosis (BV) and GBS, and a greater number of digital vaginal examinations [25]. Potential maternal complications of IAI include maternal bacteremia, postpartum endometritis, peritonitis, sepsis, and postpartum hemorrhage. Potential fetal complications include death, asphyxia, sepsis, bronchopulmonary dysplasia, cerebral palsy, and long-term neurodevelopmental disability [24, 26]. The majority of fetal and neonatal complications are significantly more common with decreasing gestational age.

Diagnosis

The common diagnostic criteria for IAI are maternal fever > 39 °C alone or maternal fever 38–39 °C with one or more of the following: maternal leukocytosis, fetal tachycardia, or purulent

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cervical drainage [24]. Maternal fever 38–39 °C in the absence of other clinical signs is termed *isolated maternal fever*. In practice the diagnosis is clinical, confirmed by histopathology only after clinical decisions are made. Amniotic fluid culture is the gold standard for clinical diagnosis, but the utility of fluid culture is limited by the time it takes for results.

Treatment

Management of IAI is straightforward. As soon as the diagnosis is made, antibiotics should be initiated, as immediate treatment with antibiotics has been shown to reduce maternal and neonatal complications [26]. For vaginal delivery, the typical antibiotic regiment includes ampicillin and gentamicin. Women with IAI who undergo a cesarean section should receive either clindamycin or metronidazole for anaerobic coverage in addition to ampicillin and gentamicin. The ideal treatment duration is unclear, but typically includes one postpartum dose of the given regimen. Vancomycin or clindamycin can be substituted for ampicillin in penicillin allergic patients. Treating maternal fever with antipyretics is also critical, providing two benefits: avoiding the adverse neonatal outcomes associated with maternal fever and potentially reducing the inclination to perform a cesarean section by resolving the associated fetal tachycardia [26]. Labor should be expedited in the setting of IAI, but cesarean delivery is only indicated for usual obstetric indications.

Meconium-Stained Amniotic Fluid

General Principles

Meconium-stained amniotic fluid (MSAF) presents as greenish- to brown-stained amniotic fluid seen at rupture of membranes. It is the result of the passage of fetal colonic material into the amniotic cavity.

Meconium-stained amniotic fluid occurs in approximately 8–15% of live births [27] and its incidence increases with gestational age. While MSAF occurs in <5% of preterm deliveries, it increases to 7–22% of term deliveries and affects 23–52% of postterm pregnancies [28].

Both prenatal stressors (fetal hypoxia and acidosis) and head or cord compression can cause vagal stimulation and relaxation of the fetal sphincter, leading to MSAF. Exposure of the meconium to the fetus can occur either in utero or at the time of the infant's first breath.

Risk factors for MSAF include postterm gestation, maternal diabetes, maternal tobacco usage, maternal respiratory or cardiovascular disease, preeclampsia, oligohydramnios, intrauterine growth restriction, low score on biophysical profile, and abnormal fetal heart rate tracing.

Meconium aspiration, intra-amniotic infection, and endometritis are all more likely to occur with MSAF [29]. Meconium aspiration syndrome (MAS) is respiratory distress in a newborn that was born through MSAF. MAS develops in 5% of infants delivered through MSAF; 95% of infant with inhaled meconium will clear it spontaneously without complication [29]. MAS is the most serious complication associated with MSAF and can lead to intubation and mechanical ventilation, pneumothorax, seizures, and death [30].

Management

It is thought that MSAF may support bacterial growth by acting as a medium for bacteria, inhibiting the bacteriostatic properties of amniotic fluid, or antagonizing typical host defense systems by diminishing the phagocytic response of neutrophils [31]. It was theorized that prophylactic antibiotics would reduce the rate of adverse events. However, no significant reductions in the incidence of neonatal sepsis, endometritis, or NICU admissions were found. And yet, there was a reduction in the incidence of intra-amniotic infections [31]. Because the rates of neonatal sepsis were similar regardless of antibiotics, there is insufficient evidence at this time to recommend administration of prophylactic antibiotics to laboring mothers with MSAF [31].

Because oligohydramnios can lead to increased cord compression and subsequently the passage of meconium, it has been theorized that amnioinfusion (AI) could be a promising therapy. While AI has been shown to reduce the risk of fetal heart rate deceleration and cesarean section in the presence of oligohydramnios, it has

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not been shown to reduce the risk of moderate or severe MAS, perinatal death, or other major maternal or neonatal disorders in the setting of standard peripartum surveillance [30]. In settings with limited peripartum surveillance, AI did reduce the risk of MAS. Currently, it is not recommended to use prophylactic amnioinfusion to reduce the risk of MAS.

Guidelines on management of the neonate were updated in 2015 and endorsed by the American Academy of Pediatrics, the American Heart Association and ACOG. These guidelines recommend against the former practice of intubation and suction in nonvigorous neonates with MSAF. Instead, infant resuscitation should "follow the same principles for infants with [MSAF] as for those with clear fluid" [32].

Shoulder Dystocia

General Principles

Shoulder dystocia is a relatively rare and usually uncomplicated condition but can become an obstetrical emergency. It occurs at delivery and is characterized by difficulty delivering fetal shoulders with downward traction of the fetal head, requiring additional maneuvers to facilitate extraction. Shoulder dystocia affects 0.2–3% of vaginal deliveries of fetuses in the vertex presentation [33]. It often results when the pubic symphysis obstructs descent of the anterior shoulder or the posterior shoulder is obstructed by the sacral promontory. If descent of the fetal head continues while the anterior or posterior shoulder remains impacted, then stretching of the nerves in the brachial plexus may occur and may result in nerve injury.

Shoulder dystocia cannot be predicted or prevented. The goal is to understand the risk factors and signs of shoulder dystocia and then remain vigilant and quickly responding when it does present. The most well-established risk factors include diabetes, fetal macrosomia (fetal weight $>$ 4000 g), and previous shoulder dystocia, as it may recur in at least 10% of subsequent pregnancies [33]. There is a paucity of literature evaluating labor complications and subsequent dystocia, but mid-pelvic operative vaginal delivery has been associated with increased risk of shoulder dystocia.

Five percent of shoulder dystocias are complicated by neonatal injury, the most common complications being brachial plexus injury and clavicular fracture. Brachial plexus injury occurs in 10–20% [33] of shoulder dystocias. While most cases are transient, and resolve completely, permanent neurologic impairment may result. Clavicular fracture and humerus fractures usually have a benign course and complete recovery. Other more serious and less common complications include pneumothorax, permanent neurological damage due to hypoxia, and death. Maternal complications primarily include postpartum hemorrhage and higher degree perineal lacerations; however, if extraordinary maneuvers such as Zavanelli or symphysiotomy are performed, complications may include uterine rupture, bladder rupture or lacerations, urethral injury rectovaginal fistula, sacroiliac joint dislocation, pubic symphysis separation, neuropathy, and stool incontinence.

Diagnosis

The diagnosis of shoulder dystocia is a clinical diagnosis based on the inability to deliver shoulders after delivery of the head. The physician should be alerted to the potential of shoulder dystocia if they notice the fetal head remains tightly applied to the vulva or retracts (turtle sign) against the perineum.

Management

As soon as a shoulder dystocia is suspected, the physician should respond by alerting the team for the need for additional assistance and preparing the patient. The mother should be alerted to the situation, discouraged from pushing, and moved toward the edge of the bed to better support the maneuvers required. Refer to Table 2 for list of maneuvers used to reduce a shoulder dystocia. When using a maneuver, the clinician should move on to another maneuver if unsuccessful after 20–30 s. In most cases, the physician has

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Table 2 Maneuvers for managing shoulder dystocia

	Initial maneuvers
McRoberts	Flex the patient's legs against the abdomen Reduces 42% of shoulder dystocias
Suprapubic pressure	Apply moderate suprapubic pressure obliquely to the anterior shoulder to adduct the shoulders into the oblique plane When combined with McRoberts – reduces 50% of shoulder dystocias
Posterior arm	Flex the fetal elbow and sweep the arm across the chest, grasp the hand and extend the arm along the side of the face, deliver the posterior arm Highly effective
Rubin	Place a hand on the posterior surface of posterior (or anterior) shoulder and rotate it anteriorly
Woods corkscrew	Place a hand on the anterior surface of the posterior shoulder and rotate the posterior shoulder 180° May combine with Rubin to increase effectiveness
Gaskin	Place mother in hands and knees and apply downward traction on posterior shoulder or upward traction on anterior shoulder Use in mothers without epidurals that can support their weight
Episiotomy	Perform an episiotomy to allow room for maneuvers, does not itself reduce shoulder dystocia
	Extraordinary maneuvers
Clavicle fracture	Press the anterior clavicle against the ramus of the pubis or pull the anterior clavicle outward to fracture the clavicle
Zavanelli	Return the fetal head to the OA or OP position, flex the fetal head and push it back into the vagina, proceed with cesarean section
Abdominal rescue	If unable to replace the fetal head into the vagina, perform a cesarean section to manually rotate the anterior shoulder into the oblique diameter; proceed with vaginal delivery
Symphysiotomy	Division of anterior fibers of symphyseal ligament – performed by individuals who have knowledge and experience in this procedure

OA occiput anterior, *OP* occiput posterior

up to 5 min to deliver a previously well-oxygenated term infant before there is an increased risk of asphyxial injury. The pH is estimated to fall between 0.01 and 0.04 pH units per minute in the interval between delivery of the fetal head and trunk. No one maneuver has been shown to be superior over another; however, ACOG recommends starting with the McRoberts maneuver as it is a "simple, logical and effective technique" [33]. Practical knowledge of all the maneuvers is important so that the most appropriate maneuver is applied in each clinical situation. Team-based simulation exercises are encouraged to improve communication and enhance familiarity with the various maneuvers.

Prevention

Prophylactic labor induction for the prevention of shoulder dystocia is not routinely recommended in women without diabetes and suspected fetal macrosomia, as it does not prevent shoulder dystocia. Prophylactic cesarean delivery is not routinely recommended unless the estimated fetal weight is >4500 g in women with diabetes or > 5000 g in women without diabetes. Both of these are ACOG level C recommendations.

Assisted Vaginal Delivery

General Principles

Assisted vaginal delivery (or "operative vaginal delivery" when referring specifically to forceps and vacuum) includes forceps delivery, vacuum delivery, and manual rotation of the fetal head. All the maneuvers aim to expedite delivery for maternal or fetal well-being and prevent the need for cesarean birth. Performed with good technique and for appropriate indications, these methods are safe and effective. Overall, rates of assisted vaginal delivery have declined over time, concurrent with an increase in the cesarean rate. However, over several decades the rate of vacuum-assisted vaginal delivery has increased while the rate of forceps delivery has dramatically

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decreased [5]. This shift may owe to the perception that vacuum delivery is less likely to cause maternal pelvic floor injury, which may be true at least in the short term [4].

Approach to the Patient

The indications for forceps and vacuum delivery include conditions that threaten the well-being of the mother or fetus: prolonged second-stage of labor, suspected or potential fetal compromise, and maternal benefit (e.g., maternal exhaustion or cardiac disease) [4, 5, 34]. Prerequisites for both forceps and vacuum application are largely the same [5]: complete dilation of the cervix, ruptured membranes, engagement of the fetal head, vertex presentation, no suspected cephalopelvic disproportion, empty maternal bladder, adequate anesthesia, and precise knowledge of fetal head position. The last prerequisite is worth highlighting, as knowledge of fetal head position is essential for safe and correct application of the assistive device. Contraindications include unknown position of the fetal head and known or suspected fetal bone mineralization or bleeding disorder (Level B evidence) [34].

The current classification system for forceps deliveries, endorsed widely by groups including ACOG, also applies to vacuum deliveries. A central purpose of its implementation was to avoid unsafe application of these techniques, as potential for harm is greater with higher fetal head position and more rotation applied to the head [35]. Outlet forceps delivery occurs with the fetal scalp visible at the introitus, the fetal skull on the pelvic floor, and application of no more than 45° of rotation. Low forceps delivery occurs with the fetal skull at or below +2 station, and midforceps delivery occurs between 0 and + 2 station. High forceps delivery is no longer viewed as being appropriate in any circumstance.

There remains a lack of consensus regarding the relative risks and benefits of forceps versus vacuum delivery. Sequential use of both should be avoided due to increased risk for significant neonatal injury [35]. Potential benefits of forceps are increased likelihood of achieving vaginal delivery [36] and its ability to achieve head rotation. However, forceps have also been associated with a trend toward more cesarean sections, as well as more third and fourth degree tears, vaginal trauma, altered continence, and facial injury [36]. The likely decreased maternal risk is a potential benefit of the vacuum, though cephalohematoma may be more common [36]. In practice, the experience of the operator will often be the primary factor when choosing between forceps and vacuum.

Technique

The technique of forceps and vacuum-assisted delivery is very similar among the numerous specific devices and well described in multiple sources. For occiput anterior presentations, correctly placed forceps travel the occipitomental diameter, with the largest portion of the blades covering the face and the greatest distance between the blades corresponding to the biparietal diameter. Correct placement of the vacuum is also essential, as this allows the fetal head to be flexed to the narrowest diameter in its passage through the pelvis. The center of the vacuum cup should be placed over the flexion point, which is in line with the sagittal suture and approximately 3 cm anterior to the anterior edge of the posterior fontanelle. Assisted delivery should be continued only if clear progress in descent is being achieved. In the case of the vacuum, rotation should not be attempted, pop-offs should be minimized to no more than three, and traction should occur for the shortest amount of time possible.

Manual rotation of the fetal head may be beneficial for occiput posterior or occiput transverse presentations. A decreased rate of operative vaginal delivery has been achieved when employing this technique, without increasing risk [37].

Cord Prolapse

General Principles

Umbilical cord prolapse (UCP) is an obstetrical emergency in which the umbilical cord passes through the cervical os in advance of the fetal presenting part (overt) or alongside the fetal

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presenting part (occult). This can cause cord compression which can lead to fetal hypoxia.

The incidence of UCP has remained stable and affects 1.4–6.2 per 1000 deliveries [38]. In the past UCP carried a high mortality rate; however, with the increased availability of cesarean delivery, the mortality rate has decreased to 10% or less [38].

There are spontaneous and iatrogenic risk factors for UCP. Spontaneous UCP can occur in uncomplicated pregnancies and is related to conditions that prevent the fetus from properly engaging in the pelvis or abnormalities of the umbilical cord itself including: fetal malpresentation (most common), polyhydramnios, preterm delivery, preterm premature rupture of membranes, multiple gestation, fetal anomalies, grand multiparity, cord abnormalities (higher risk of prolapse with a thin cord), birth weight less than 2500 g (although some authors quote <1500 g) [39], and spontaneous rupture of membranes (57% of cases occurred within 5 min of rupture) [40]. Iatrogenic causes include artificial rupture of membranes without an engaged presenting part, attempted rotation of the fetal head, amnioinfusion, external cephalic version in patient with ruptured membranes, placement of an intrauterine pressure catheter or fetal scalp electrode, and placement of a cervical ripening balloon catheter. These risk factors are usually maneuvers performed by the clinician on the labor and delivery floor and do not increase morbidity and mortality due to the availability of a quick response by the clinician.

Diagnosis

UCP is diagnosed clinically by the umbilical cord being palpable or visible in the vagina. The clinician may also notice a severe and sudden drop in the fetal heart tones (FHT) or variable decelerations. It is worth noting that these FHT changes are not always initially seen.

Prevention

Given that membrane rupture, whether spontaneous or artificial, is a risk factor for cord prolapse, it is recommended that care be taken when considering artificial rupture of membranes. If the head is well applied to the cervix, amniotomy may be safely performed. When the fetal head is ballotable, amniotomy should be delayed or performed in a controlled manner to avoid sudden decompression.

Management

Umbilical cord prolapse can quickly compromise the fetus which can lead to disability and death. The primary management of UCP is immediate delivery and is usually done via emergent cesarean section. Until delivery can be performed, the goal is to alleviate pressure on the umbilical cord. This is done by:

- Funic decompression – the clinician places two fingers or the palm on the fetus' presenting part and elevates it.
- Trendelenburg or knee-chest position – place the mother in Trendelenburg position or knee-to-chest position to allow gravity to assist in alleviating pressure on the umbilical cord.
- Foley catheter (first described in 1970 by Vago) – bladder instilled with saline to allow the distended bladder to provide an upward pressure on the fetal presenting part.

The fetus should be continuously monitored until delivery. Neonatal outcomes in cases of UCP are generally good when delivery can be accomplished within 30 min.

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Postpartum Care

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Tanya Anim, Rahmat Na'Allah, and Craig Griebel

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Introduction

Childbirth and the postpartum period constitute an exciting yet challenging time for the mother, newborn, and family members. This includes physiological, physical, and psychosocial changes which many new mothers transition through uneventfully. However, this period can also pose overwhelming challenges with associated health issues. Hence, the importance of comprehensive prenatal, intrapartum, and postpartum care along with anticipatory guidance cannot be overemphasized.

Immediate Postpartum Care

The Golden Hour: Maternal-Infant Bonding

The "golden hour" is the immediate 60 min after childbirth. In the past when more babies were born outside the hospital, placing the newborn directly skin to skin on the mother's chest or abdomen was necessary for the infant's survival. It continues to be the practice in many developing countries. In industrialized nations, it had become common practice for infants to be immediately whisked away for "transition" which includes a check of vital signs, maintaining temperature by placing them on the warmer, medications, immunizations, and sometimes a bath. However, it has since been shown that it is in the best interest of the mother-baby dyad that skin-to-skin contact (SSC) be initiated in that time. A Cochrane review of 34 randomized trials involving 2177 mothers and newborns concluded that babies who were immediately exposed to SSC cried less, had better cardiorespiratory function, and had better interactions with their mothers. They also were more likely to breastfeed in the first 1–4 months of life and breastfed longer when compared to babies who were not exposed to SSC. There were no negative effects of SSC found in these trials [1].

Formation of a strong bond between the mother and infant has been shown in multiple studies to enhance the cognitive and neurobehavioral development of the child. Recommendations from early research on maternal-infant bonding include delaying newborn procedures such as medication application, initiating breastfeeding immediately after birth, rooming in, and encouraging parents to interact with their babies [2].

Babywearing, the use of carriers and/or slings of many kinds to secure a baby against a caregiver's body, may be used to help facilitate skin-to-skin contact when done safely [2]. This practice should be encouraged and supported whenever possible.

Immediate Postpartum Contraception

One option that may be offered for the immediate postpartum period is insertion of a long-acting reversible contraceptive (LARC device) [3]. Immediate placement of a LARC has been shown to decrease the risk of short interpregnancy intervals (<18 months from time of delivery to subsequent pregnancy) [3]. Options include the copper or levonogestrel IUD. Subcutaneous placement of an etonogestrel implant is also an option.

Of note, the placement of an IUD immediately postpartum is associated with increased risk of expulsion compared to placement of the device at 6 weeks postpartum. However, consideration may be given to the fact that some patients may have difficulty attending their outpatient postpartum appointments.

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Promotion of Breastfeeding

Part of the benefit of early maternal-infant bonding is the initiation and continuation of breastfeeding. Family physicians, obstetricians, pediatricians, and other members of the medical team all play a significant role in ensuring the success of breastfeeding. Discussion about breastfeeding should begin in the prenatal period. Emphasizing the immediate and long-term benefits of breastfeeding on the mom and baby early in the prenatal period is optimal. The benefits of breastfeeding on the infant and mother have been demonstrated by scientific evidence, hence all major maternal-child health organizations recommend exclusive breastfeeding in the first 6 months of life and continued through 1–2 years of age [4]. Early anticipation of barriers to breastfeeding will help in providing the necessary support for the new mother and her family. During the first several weeks of breastfeeding, infants should be nursed at least 8–12 times in a 24 h period on demand [5]. The Academy of Breastfeeding Medicine recommends creating a breastfeeding-friendly office; understanding the effect of cultural influence on families and communities; and integrating breastfeeding promotion, education, and support throughout the prenatal period [6]. Current evidence suggests that the Baby Friendly Hospital Initiative and the "Ten steps to Successful Breastfeeding" are proven and effective measures to ensure breastfeeding initiation, duration, and exclusivity [7]. Hospitals that are certified as being "baby friendly" have the highest breastfeeding rates [5, 8].

Contraindications to Breastfeeding

There are very few absolute contraindications to breastfeeding or feeding infants expressed breast milk. These include mothers living with HIV, those infected with human T-cell lymphotropic virus (HTLV) or Ebola. In addition, infants should not ingest the breast milk of mothers using illicit drugs. Infants with galactosemia should also not ingest breast milk.

Breastfeeding should be suspended temporarily in women with active brucellosis, those receiving radiopharmaceuticals, and those with active herpes simplex lesions of the breast. Those who should not be in contact with the baby but can feed expressed breast milk include women with active tuberculosis or varicella [9, 10].

Although most medications are compatible with breastfeeding, sources such as Infant Risk (https://www.infantrisk.com/infantrisk-center-apps) and The Drug and Lactation Database (LactMed) (https://www.ncbi.nlm.nih.gov/books/NBK501922/) should be referenced prior to counseling mothers about breastfeeding while taking medications. Breastfeeding is absolutely contraindicated in mothers taking certain medications that include radioactive iodine [11], and antineoplastic drugs such as cisplatin [11].

When counseling women about breastfeeding risks, a discussion of the risks of NOT breastfeeding should also be touched upon. Mothers should be reminded that breastfeeding is the biological norm and preferred method of infant nutrition, as opposed to human milk substitutes (formula) [9].

Important Noncontraindications

It is imperative that family physicians remain knowledgeable about true contraindications to breastfeeding. For example, mothers who are Hepatitis B or Hepatitis C positive may still be able to breastfeed [7]. Patients taking stable doses of methadone may breastfeed as well, regardless of their current methadone dose [12]. Additionally, patients who use marijuana may also breastfeed, as long as it is certain that adulterants are not present in the drug [9]. These decisions should be discussed with the patient so that they understand the true risks being posed to the infant including consideration for the risks is poses to not breastfeed. Additionally, mothers who choose to consume alcohol (up to 8 oz. or wine or 2 beers in a day) while lactating may also continue breastfeeding [12]. They should not be instructed to "pump and dump" and should instead be counseled to breastfeed prior to drinking and

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then wait until at least 2 h after drinking to breastfeed when their blood alcohol level is likely to have diminished.

Similarly, it is not necessary to cease or otherwise interrupt breastfeeding after most radiologic examinations including ultrasounds, chest X-rays, CT scans, or MRIs, including those in which iodinated or gadolinium contrast media are used, as long as no radioisotopes have been used [13]. The most recent guidelines should be referenced prior to making recommendations to lactating patients receiving imaging studies.

Postpartum Complications

Postpartum Hemorrhage

Various definitions for postpartum hemorrhage (PPH) have been proposed. The most commonly used definition is the loss of 500 ml of blood after a vaginal delivery or the loss of 1000 ml after a Cesarean delivery. However, blood loss estimates often underestimate the actual blood loss at a delivery. Another suggested definition is the drop in the hematocrit of 10% or more, but if blood loss is ongoing, the decline in hematocrit may underestimate the actual blood loss [14].

Postpartum hemorrhage has been reported to occur in up to 18% of deliveries, with approximately 3% of births resulting in severe postpartum hemorrhage. PPH is the most common cause of maternal morbidity in developed countries [7]. Complications after PPH include hypotension, difficulty with breastfeeding and caring for the newborn, extreme fatigue, and blood transfusion reactions if a transfusion is required. Hemorrhagic shock after postpartum hemorrhage can lead to Sheehan's syndrome (pituitary necrosis) [7].

There are a number of risk factors for PPH, including a past history of PPH, prolonged labor, augmented labor, overdistended uterus, chorioamnionitis, preeclampsia, and operative delivery [14]. However, many patients who develop PPH have no risk factors, so providers must be alert to this complication at every delivery.

The active management of the third stage of labor (AMTSL) has long been recognized as an effective method for the prevention of PPH. An intravenous infusion of oxytocin (20 units) is widely recommended and is the most important component in the AMTSL. It can be administered as soon as the anterior shoulder is delivered but no later than after placental delivery. Most protocols for the AMTSL have now discontinued immediate cord clamping, since a delay in cord clamping of at least 30–60 s (assuming the newborn does not require resuscitation) has been shown to improve the hematologic status of newborns. Controlled cord traction is often recommended and has been shown to result in a small reduction in blood loss. Routine uterine massage is often performed, but a World Health Organization guideline recommends against this practice, while stipulating that the uterine tone should be routinely assessed [15].

The most common cause of PPH is uterine atony (70%). Trauma is the second-most common cause, at 20%. Trauma can include perineal, vaginal wall, and cervical lacerations; vaginal or vulvar hematomas; uterine inversion; and uterine rupture. Retained placental tissue is the next most common cause, at 10%. The final and least common cause of PPH at a rate of less than 1% is coagulopathy. The coagulopathy may be due to an inherited coagulopathy that was identified before delivery or due to a coagulopathy that develops as a result of a complication of pregnancy or delivery [16].

The initial management of uterine atony involves bimanual uterine massage. If this is not successful, then uterotonic medications should be administered. Oxytocin may already be infusing if it was started as part of the active management of the third stage of labor. If it has not already been initiated, administration of oxytocin 10 units IM or 20–40 units by intravenous infusion should be initiated. If the atony persists, second-line medications include misoprostol (Cytotec), 800–1000 microgram PO, SL, or PR; methylergonovine (Methergine), 0.2 mg IM every 2–4 h; or carboprost (Hemabate), 0.25 mg IM or intramyometrially every 15 min up to 8 doses [16].

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The clinician can evaluate for trauma as a cause of PPH by inspecting the vulva, vagina, and cervix for lacerations and hematomas [16].

The placenta usually delivers within 10 min of delivery of the baby. Visual inspection of the delivered placenta can provide evidence that the placenta delivered intact but does not rule out retained placental tissue. Retained placental tissue is usually easily removed by performing a finger sweep of the uterus with gauze. If placenta accreta, increta, or percreta is present, this can result in difficulty in removal of the placenta and significantly increases the risk for severe postpartum hemorrhage [16].

If a patient has been previously diagnosed with a coagulopathy, measures may already be in place to treat the disorder. If no coagulopathy has been diagnosed in a patient experiencing a PPH and other causes excluded, evaluation of the patient with a complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen level is indicated [16].

If a patient does not respond to basic measures for the management of PPH, more drastic measures may be required. It is recommended that hospitals have an established protocol that can be activated in cases of severe PPH. This involves a multidisciplinary approach between the physician, nursing personnel, blood bank, and laboratory [15]. Specialty consultation may include an obstetrician, intensivist, and interventional radiologist. Fluid resuscitation is initiated, followed by transfusion of packed red blood cells (PRBCs) and, if necessary, fresh frozen plasma and cryoprecipitate. Placement of a Bakri balloon to provide uterine tamponade should be considered. Other drastic measures include uterine artery embolization, recombinant factor VIIa, placement of B-Lynch sutures, or hysterectomy [14].

Postpartum Gestational Hypertension, Preeclampsia, and Eclampsia

The onset of gestational hypertension, preeclampsia, and eclampsia usually occurs before delivery but can also occur in the postpartum period. Diagnosis, treatment, and management of these conditions are the same as before delivery and are discussed elsewhere. Onset of these conditions can occur up to 6 weeks after delivery [17].

Postpartum Infection

Postpartum patients are at risk for a number of postpartum infections, including endometritis, wound infection, urinary tract infections, mastitis, and pneumonia. Sepsis is diagnosed when the postpartum patient develops systemic symptoms and may progress to septic shock, which has a high rate of morbidity and can also cause maternal death. The presence of fever (100.4 °F (38.0 °C) or greater) after delivery should prompt an evaluation for infection. Evaluation should include a CBC; a catheterized urine specimen for urinalysis and culture; and a physical exam. Further testing such as a blood culture, chest X-ray, wound culture, and CT scan or ultrasound of the abdomen and pelvis will be dictated by the patient's symptoms, lab testing, and physical exam. The value of a culture from the endometrium is limited and not usually indicated [18]. The white blood cell count can be mildly elevated after a normal delivery, so it must be interpreted with caution. Fever can also be caused by medication, so the patient's medications should be reviewed.

Endometritis is the most common cause of postpartum infection. The incidence of postpartum endometritis is approximately 5% after vaginal and 10% after Cesarean delivery [19]. Although preoperative antibiotic prophylaxis reduces the rate of endometritis [20], other risk factors include prolonged labor, prolonged rupture of membranes, intrauterine monitoring, and multiple vaginal examinations. In addition to fever, affected patients often have symptoms of malaise, tachycardia, uterine tenderness, and foul-smelling lochia. Postpartum endometritis is usually polymicrobial, and common causative organisms include Group B *Streptococcus*, *Enterococcus*, gram-positive anaerobes, *Staphylococcus* species, and gram-negative bacilli. Intravenous clindamycin and gentamicin has been shown to have fewer treatment failures than other regimens [21]. Intravenous antibiotics are

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continued until the patient has been afebrile for 24–48 h, the WBC count has normalized, and the patient is otherwise clinically stable [19]. There has not been shown to be any benefit of continuing oral antibiotic therapy after intravenous antibiotic therapy has been discontinued [21].

Postpartum wound infection is diagnosed by redness, swelling, drainage, and/or pain at the site of surgical or traumatic wounds. Risk factors for post-Cesarean wound infection include prolonged labor/prolonged rupture of membranes, chorioamnionitis, obesity, and prolonged surgery [20]. If an abscess is present, this should be opened and drained. A culture should be obtained from any drainage that is present or if an abscess is opened. Causative organisms typically originate from skin flora or by spread from the amniotic cavity (if the patient delivered by "Cesarean" section) [20] and include *Staphylococcus aureus*, *Streptococci*, and gram-negative bacilli.

Urinary tract infections are diagnosed in the same way as general medical patients by the presence of pyuria, usually accompanied by positive nitrate testing on dipstick analysis. Urinary tract infections in the postpartum period are treated as in general medical patients. Similarly, pneumonia is diagnosed with a clinical exam and confirmatory chest X-ray. Treatment is the same as in a general medical patient, with attention to antibiotic selection if the woman is breastfeeding.

Mastitis is diagnosed by physical exam findings of redness, swelling, and tenderness of one breast, usually occurring in the first 3 months postpartum. No blood work or diagnostic testing is needed in uncomplicated cases. Mothers should be encouraged to continue breastfeeding since uncomplicated mastitis does not pose a risk to the infant and continuing milk flow is an important component of treatment [22]. Mastitis is usually caused by *Staphylococcus* aureus, Group A or B Streptococci, or Hemophilus organisms. An oral antibiotic with coverage for *Staphylococcus aureus* is usually employed, typically dicloxacillin, cephalexin, or amoxicillin/clavulanate unless methicillin-resistant *Staphylococcus aureus* is suspected, in which case clindamycin may be considered. Breast abscess may arise as a complication of postpartum mastitis. Treatment involves drainage of the abscess and usually administration of antibiotics. In most cases, breastfeeding may continue.

Postpartum Preventive Care

Immunization

According to the advisory committee on immunization practices, all pregnant women should be immunized with Tdap between 27 and 36 weeks, irrespective of the patient's prior immunization history. Since 2010, there has been a resurgence of pertussis with the highest incidence in 2012. Over 2000 of the cases were among infants, 15 of whom died [23]. Vaccination during pregnancy will prevent hospitalization and death from pertussis. However, if the immunization is not received during pregnancy, it should be provided postpartum [23]. Additionally, MMR should be administered as soon as possible after delivery if the mother was found to be nonimmune to rubella [24]. At the time of this publication, there are no available safety data regarding the risk of the COVID-19 vaccine on lactating patients or their breastfed infants. Shared decision-making should be employed with these patients, to help them decide the best option for them, particularly those at high risk for exposure to COVID-19 and those at high risk for complications should they contract the virus [25].

RhoGAM

The Rh immune globulin (RhoGAM) is given to an Rh-negative mother at 28 weeks of gestation if the Rh status of the baby is unknown, those who give birth to an Rh-positive baby, or any Rh-negative patient after a miscarriage. The purpose is to prevent immune response occurring from alloimmunization which can lead to hemolytic disease of the newborn in subsequent pregnancies. The typical dose is one vial of 300 mcg of RhoGAM within 72 h of delivery if there is no evidence of fetal red blood cells in maternal blood. Otherwise, the quantity of estimated fetomaternal

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hemorrhage determines how many vials of RhoGAM are given [26]. The risk of rhesus alloimmunization can decrease from 1–2% to 0.1% if RhoGAM is given at 28 weeks gestation and postpartum [27, 28]. It is still acceptable to give RhoGAM up to 28 days postpartum if it had not been not given within 72 h of delivery [29].

Postpartum Office Visit

The postpartum period begins an hour after delivery of the placenta though the subsequent 12 weeks (sometimes termed the fourth trimester) [30]. It was popular convention for the postpartum office visit to take place at 6 weeks postpartum. However, in 2018, ACOG published an updated Committee Opinion encouraging for all women to have contact with their maternity care provider either in person or by phone within 3 weeks postpartum, with ongoing support at intervals to be determined by the patient and her physician. In addition, the opinion recommends a comprehensive postpartum visit no later than 12 weeks after delivery. The physician should address issues like breastfeeding, postpartum depression, complications such as urinary incontinence, constipation, sexuality, and contraception. However, for some women, waiting till 6 weeks might be too late [31]. Selected patients may benefit from postpartum office visits as early as 2 weeks after discharge. The discontinuation rate for breastfeeding at 2 weeks is as high as 25%, with many women citing lack of confidence, support, and perceptions of insufficient milk production [32]. Early visits and encouragement from the clinician may play a significant role in rates of breastfeeding continuation. Fifty-five percent of women cited individualized encouragement by their clinician as a reason for continuing breastfeeding until 12 weeks postpartum [33]. Women in the adolescent age group, recent immigrant status, lack of social support, mental health problems, and physician judgment are some indications to consider an earlier visit [31].

In the early postpartum period, issues such as abnormal vaginal bleeding, anemia, perineal pain, constipation, breast pain/engorgement, fever, and contraception should be addressed. Prior to discharge, it is important to evaluate patient's mood, support, and readiness for discharge. A detailed anticipatory guidance regarding postpartum blues and risk for depression is very important [31]. It is the family physician's role to provide support and encouragement for the entire family. Patients should have access to a contact that they can call for support and advice as necessary. At the 3–6 week visit, discussion should surround breastfeeding support, anemia, contraception, libido, and sexuality. Health maintenance, lifestyle modification, and immunization are often addressed after 6 weeks [28]. Physicians provide information and guidance about sexuality in pregnancy and childbirth in fewer than 30% of cases [34]. Sexuality after childbirth can be affected by vaginal dryness, pelvic floor dysfunction, and decreased libido [35]. There is need for education of new parents both before and after childbirth as cultural beliefs and myths continue to play significant roles in sexuality in pregnancy and after childbirth.

Women with a diagnosis of gestational diabetes during pregnancy also require close follow-up in the postpartum period. In the immediate postpartum period, diabetic medications are generally discontinued. Women are often advised to discontinue home blood glucose monitoring. However, they should undergo a 75 g 2-h fasting oral glucose tolerance test or fasting serum glucose check between 4 and 12 weeks postpartum [28, 30].

Postpartum Contraception

If not already completed in the immediate postpartum period, contraception (if desired) should be discussed and offered at the comprehensive postpartum visit. The choice of contraception should be individualized based on a number of factors including breastfeeding, patient's age, parity, previous contraceptive experience, birth spacing, partner's plan, health status, and accessibility. Birth spacing is not just important to mothers but also to their children and to the society in general. The longer the interval between births (especially between 27 and 32 months), the lower the risk of

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major maternal complications such as bleeding, anemia, infection, and even death in subsequent pregnancies [36]. A 3 year interval between births has been shown to decrease neonatal and post-neonatal mortality for the subsequent child [37].

Breastfeeding is a form of contraception. The lactation amenorrhea method (LAM) is an effective mode of contraception up to 6 months in a woman who exclusively breastfeeds and has not resumed menstruation [38]. Once supplemental feeding is introduced or menstrual bleeding starts, an alternative form of contraception becomes necessary [39]. There is much controversy on the safety of contraceptive agents in breastfeeding women, especially regarding milk volume, and the passage of exogenous hormones into breast milk. Many studies have shown decreased milk supply as a major side effect of using combined oral contraception (COC) prior to 6 weeks. It has been found that there is a statistically significant reduction in milk volume among COC users when compared to users of progestin-only contraceptive pills [40].

Postpartum Contraceptive Options

There are a plethora of options available for patients postpartum. Shared decision-making should be employed when helping patients decide which option is right for them. As with any patient considering their contraceptive options, their needs should be discussed in terms of convenience, cost, and medical risk factors. Lactation status should also be a consideration.

The US Medical Eligibility Criteria for Contraception (MEC) [41] provides guidance on which contraceptive methods are most appropriate for a patient in specific situations. Contraceptive options are classified under four categories in the setting of each condition in the US MEC. Category 1 is defined as contraceptives that can be used without restriction in a particular situation, Category 2 denotes that benefits are likely outweigh any theoretical risk, Category 3 denotes theoretical or proven risks that are likely to outweigh benefits, and Category 4 include medications that are considered to pose an unacceptable risk.

Table A1 of the US MEC contains the summary of changes in recommendations made in the 2016 edition. Many of these changes therein pertain to recommendations for use in the postpartum period. Generally speaking, progestin implants, depo-medroxyprogesterone acetate, and progesterone-only pills are classified as Category 2 forms of contraception for breastfeeding patients up to 30 days postpartum. Combined hormonal contraceptives (CHC) (pills, vaginal contraceptives, patches, and the like) are rated as Category 4 in the breastfeeding patient less than 21 days postpartum (those without yet well-established milk supply, and during a time when the risk for VTE is significant), Category 3 for 21–42 days postpartum, and Category 2 thereafter.

The recommendations are different for patients who are not breastfeeding. Progestin implants, depo-medroxyprogesterone acetate, and progesterone-only pills are all rated as Category 1 at any time in the postpartum period for those not breastfeeding. CHCs remain a Category 4 for patients in the 21 days after delivery for non-breastfeeding patients. CHCs are Category 3 in the 21–42 day postpartum period for patients with significant VTE risk factors (such as age >35 or previous VTE), whereas Category 2 in those at average risk for VTE in the 21–42 day postpartum period. CHCs are Category 1 for all patients greater than 42 days postpartum who are not breastfeeding.

Copper IUDs and progestin-containing IUDs are rated as Categories 1 and 2, respectively, within 10 min following delivery in the breastfeeding patient while they are both Category 1 in the nonbreastfeeding patient. For patients who are either breastfeeding or not-breastfeeding, the risks are considered to be similar after 10 min. For patients 10 min to 4 weeks postpartum, IUDs are a Category 2. After 4 weeks IUDs are considered Category 1 for both groups.

Postpartum Depression

Postpartum depression occurs in approximately 13% of all new mothers [42]. Therefore, routine screening for postpartum depression in all mothers is recommended. The Edinburgh

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Postnatal Depression Scale is the most widely used screening tool. Risk factors for postpartum depression include previous postpartum depression, a previous history of depression, poor social support, and psychosocial stressors [43]. Typical symptoms include depressed mood, anhedonia, decreased energy, feelings of guilt, psychomotor retardation, and suicidal ideation. Physicians should measure thyroid-stimulating hormone levels in women with suspected postpartum depression [43]. Psychosocial and psychological interventions including peer support, nondirective counseling, cognitive behavioral therapy, and interpersonal psychotherapy appear to be effective in reducing symptoms of postpartum depression [42]. Selective serotonin reuptake inhibitors have also been shown to be effective in the treatment of postpartum depression [43].

Postpartum Thyroid Dysfunction

The postpartum period is a common time for the development of thyroid dysfunction. The most common postpartum thyroid condition is thyroiditis, affecting approximately 8% of postpartum women [44]. There is currently insufficient evidence to recommend universal screening of all women for postpartum thyroiditis; however, it is recommended that all women with postpartum depression be screened for thyroid disease with a TSH, free T4, and thyroperoxidase antibody testing [45].

The typical clinical course for women who develop thyroiditis is to initially develop transient thyrotoxicosis between 2 and 6 months postpartum. This is usually asymptomatic. Thyrotoxicosis is often followed by hypothyroidism, usually returning to the euthyroid state by the end of the initial postpartum year. Postpartum women with symptomatic thyrotoxicosis should be treated with beta-blockers [44]. Following resolution of the thyrotoxic phase, the TSH should be monitored every 2 months to screen for hypothyroidism. Hypothyroidism may require treatment with levothyroxine. If treatment with levothyroxine is initiated, tapering off of the medication can usually be initiated in 6–12 months, with intermittent monitoring.

Postpartum Venous Thromboembolism

Increased risk for venous thromboembolism continues after pregnancy and actually increases during the postpartum period [46]. In addition, the risk for pulmonary embolism is higher in the postpartum period than during pregnancy [46]. Risk for venous thromboembolism is greatest in the first 3 weeks postpartum, returning to baseline at 12 weeks postpartum [47]. Older age, obesity, smoking, Black race, Cesarean delivery, preeclampsia, maternal hemorrhage, anemia, and postpartum infection are all risks for venous thromboembolism. Diagnosis of postpartum lower extremity venous thromboembolism can be made difficult by the common occurrence of lower extremity edema. However, unilateral leg swelling (particularly left sided), redness, and pain should increase the suspicion for venous thromboembolism. Venous compression Doppler ultrasound is the recommended diagnostic test to evaluate for a lower extremity venous thrombus. Treatment with warfarin is recommended and is safe to use in a breastfeeding mother. Low-molecular-weight heparin can be used as a bridge until the prothrombin time is therapeutic for the requisite period of time. Dyspnea and tachypnea are the most common presenting symptoms of pulmonary embolism. Postpartum pulmonary embolism has a relatively high mortality rate [48].

Health Equity and Standardization of Maternity Care

Racial and ethnic health disparities are pervasive in all areas of medicine. One of the most significant areas for these disparities is in maternity care [49]. Black women are 3 to 4 times more likely to die as a result of circumstances surrounding pregnancy. Health disparities occur along the entire trajectory from preconception to postpartum care.

In the USA, racial and ethnic minorities suffer greater risks of postpartum hemorrhage and puerperal infections than do their White counterparts.

One strategy that has been advanced to combat these disparities is standardization of care. The

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use of tools such as safety bundles, standardized protocols, and standard triggers have been shown to improve care, particularly care that is provided to women of color [49].

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Part IV

Care of the Infant, Child, and Adolescent

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Genetic Disorders

15

Mylynda Beryl Massart

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Introduction

This chapter will serve as an introduction to genomic medicine for the family medicine physician. Historically, family medicine physicians have

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recognized and managed many common genetic syndromes such as Trisomy 21, Klinefelter syndrome, Neurofibromatosis, and Huntington's chorea which exist in the population. In the current era of molecular and genomic medicine, there are an ever-increasing set of competencies to adequately assess, interpret, and counsel our patients regarding their genetic contributions to the detection, prevention, and management of disease. Family Physicians have an increasing responsibility to be able to accurately assess genetic familial risk and provide guidance in a vast array of genetic health-care choices including prenatal testing, cancer risk assessment and intervention, medication choices based on genetically determined variations in metabolism, and the exponentially increasing numbers of clinical and direct-to-consumer genetic testing available. The goal is that this genetic data is then integrated into personalized medicine plans for chronic disease prevention.

Despite the existence of medical genetics specialists, and genetic counselors, studies have shown that patients prefer genetic risk assessment and counseling be done by their primary care provider [1]. In addition, as molecular medicine expands away from rare highly penetrant single-gene disorders to the complex interplay of multiple genes, environmental, and lifestyle choices, there will not be an adequate supply of medical geneticists and genetic counselors to meet the growing need or geographic distribution of the population. Therefore, much of the management and prevention of heritable disease will be left to the primary care physician, who is ideally suited for this role [2]. In addition, legal precedent has now been set for negligence claims when providers have failed to identify increased risk for heritable disease, specifically cancer [3].

To address these advancements in genetics, the American Academy of Family Physicians (AAFP) has outlined recommended competencies in medical genetics [4]. In addition, the Genetics in Primary Care Institute [5] developed initially with pediatric primary care in mind has narrowed many of these competencies down to seven key roles for the primary care physician (see below). This chapter will provide the basic tools and references for additional resources to begin integrating these genetic competencies into practice.

Seven Key Roles [5]

1. Evaluate through screening and surveillance: Use family health history for primary prevention of chronic illness and to identify a patient's need for increased surveillance
2. Educate patients and their families: Discuss the importance of screening, early diagnosis, and how genetic tendencies may be present with an acute manifestation of the disease
3. Explain the results: Review and discuss the meaning of screening, test results, and what to expect from genetic consultation and referral
4. Make appropriate referrals: Provide information based on clinical history and ensure adequate follow-up for patients
5. Coordinate care with a subspecialist: Initiate a co-management plan, including treatment and diagnostic testing when indicated
6. Counsel patients and families: Help them understand and adapt to the implications of a genetic diagnosis
7. Provide long-term follow-up and care: Continue to support patients and families and provide primary care through an ongoing relationship within the medical home

Basic Science of Genetics

Terminology

Within normal cellular function, genes are the basic physical unit of inheritance which contains the information to encode a protein. The genes are arranged in discrete units on chromosomes which consist of a long double-stranded DNA molecule [6]. There are approximately 26,000 genes arranged over the 22 pairs of autosomes and one pair of sex chromosomes in the nucleus of a human cell. At conception, each parent contributes one copy of each of their autosomes and one sex chromosome to the subsequent offspring [6]. This collection of genes is known as an individuals' genotype. The chromosomes are then packaged into compressed packages called

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chromatin which allows the DNA material to be condensed into the nucleus. Changes in chromatin structure can affect gene expression and are one mechanism of variation of phenotype without alteration of the genotype, called epigenetic variation. Via the process of gene expression, the cell reads the sequence of DNA three bases at a time and assembles the amino acids together to form proteins. These proteins are then responsible for all cellular functions.

When the normal cellular process is disrupted, mutations or variations in the genetic code develop. These can occur by copying errors during cell division, from exposure to ionizing radiation, chemicals, or viruses. When an error occurs in a germ line cell (sperm or ova), the mutation can be passed on to subsequent offspring. If the mutation occurs in a somatic cell elsewhere in the body, the mutation is not passed on to subsequent generations. Mutations can occur by a single-base pair change, or by deletions, duplications, or rearrangements of small or large sequences of DNA. These alterations in genotype (genetic makeup of a cell) can then manifest in several different phenotypes (observable characteristic or trait). It can result in no effect, called a silent mutation, or in failure to produce a protein, or to produce a modified version of the protein which could impact its function and even excess production of a protein. Some variations may result in a nonviable fetus, others in a genetic syndrome or increased disease risk or susceptibility. The most common variations seen are known as single-nucleotide polymorphisms (SNPs). These are variations of a single-base pair and can be tracked for correlation with disease manifestation, drug response variability, and other phenotypes.

Once genetic variation occurs in the germ line, it can be passed on through several different modes of inheritance. Genetic diseases can be autosomal dominant, meaning that individuals who inherit one mutated copy of a gene will manifest the disease. In this type of inheritance, each affected individual has at least one affected parent, and the disease tends to be seen in each generation of an affected family [7]. De novo mutations may also be seen, where the disease appears initially only in the index case. Autosomal recessive disorders affect individuals who inherit two copies of a mutated gene, one from each parent. The parents are carriers of the mutation since they are heterozygous (possess only one copy of the mutated gene) and are unaffected. Mitochondrial disorders are mutations in the mitochondrial genome which are only inherited from the mother. Mitochondrial diseases affect both males and females and appear in every generation of an affected family. X-linked disorders can be dominant or recessive. X-linked dominant mutations affect females more than males since there is no male-to-male transmission. X-linked recessive mutations, however, affect males more than females since males only need to inherit one copy of the mutated gene from their mother. While most syndromes are single-gene disorders, the expressions of these conditions are often strongly influenced by multiple factors. These may include polygenic risk scores which are combinations of mutations in multiple genes, as well as the impact from epigenetics through chromatin compaction and environmental influences. In addition, many genetic syndromes and diseases have incomplete or variable penetrance, where the genetic trait is not expressed or fully expressed in all individuals carrying the mutation [7]. All of these factors may affect the conditions encountered by the family medicine physician in the clinical setting.

Family History Taking/Genogram

In an ideal office situation, each provider would be able to take a detailed family history of each new patient as they establish care and then periodically review and update this information. With respect to genetic risk assessment, this is best done by creating a pedigree or genogram. The basic pedigree would assess at least three generations and include any relevant medical problems, age of death, and ethnic origins. The advantage of the genogram is the additional overlay of the psychosocial information of the family structure and each individual contribution. The result is a visual aid that may help to detect increased risk for diseases and any associated modifiable risk factors [8].

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The pedigree should include the current age of each family member and the age of onset of each disease or diagnosis and the age and cause of death for the patient and the first-, second-, and third-degree relatives on both the patients maternal and paternal lineage [3, 8, 9]. The use of standardized symbols and diagrams allows for rapid recognition of patterns of disease transmission (see Figs. 1 and 2). The identification of two or more individuals on the same side of the pedigree with the same disease, or earlier onset of disease than expected, should raise a red flag for possible genetic pattern of inheritance and increased risk [5]. Identification of consanguinity will also increase the risk due to the higher degree of shared genetic material [8, 9]. Specific ancestral origins are also important to identify due to genetic variation among geographical and ethnic subpopulations. This is especially important in identifying the need for possible prenatal screening. The largest ethnic-specific prenatal panel is the Ashkenazi Jewish genetic panel which tests for carrier status for Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, glycogen storage disease Type 1a, maple syrup urine disease, mucolipidosis IV, Niemann-Pick disease, and Tay-Sachs disease [10].

Common Chromosomal and Genetic Disorders

Most patients with common chromosomal and genetic disorders will be diagnosed shortly after birth or early in life. However, all family medicine physicians should be able to recognize common dysmorphic features or raise concern in the presence of multiple physical anomalies or cognitive impairment and coordinate referral to a genetic specialist for diagnosis and management recommendations. There are numerous references available to allow the primary care physician to manage individuals with these known genetic syndromes in the context of their overall health care and the unique medical needs related to their diagnosis. After initial diagnosis, these patients can be effectively managed by the family

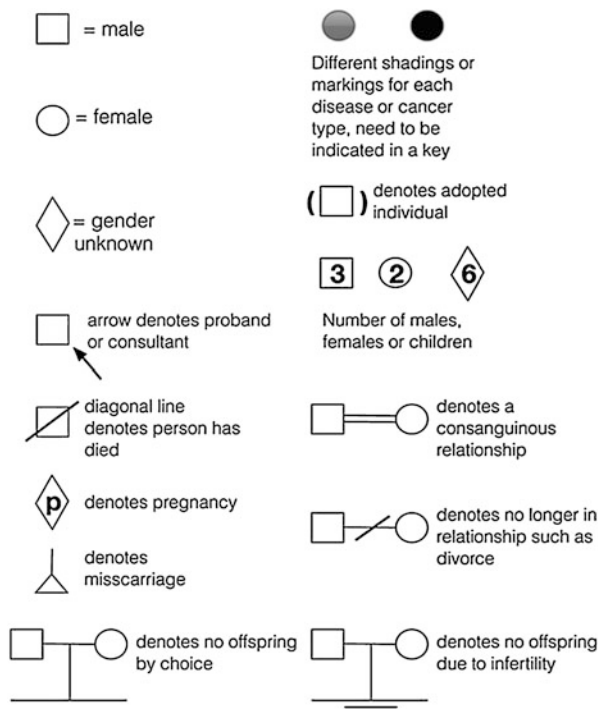
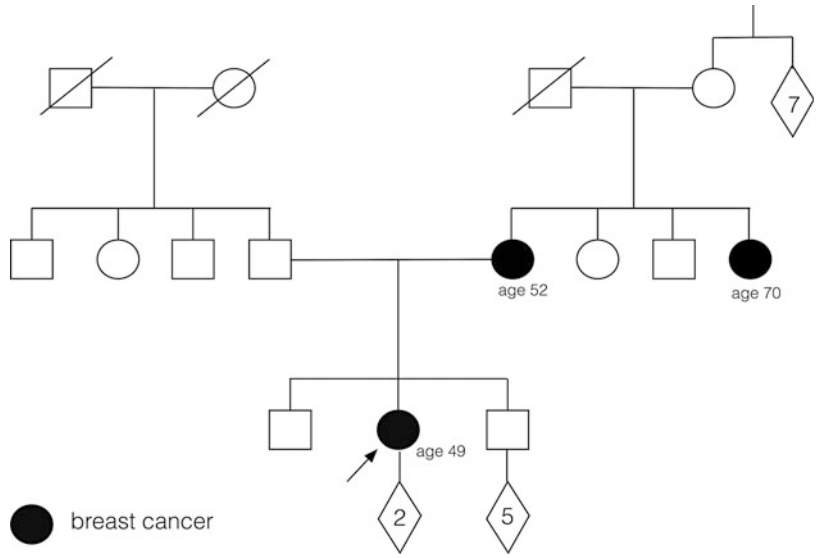


Fig. 1 Standard pedigree symbols

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Fig. 2 Sample pedigree



physician to coordinate any additional interventions, specialty care, and therapies through their primary care medical home (see Table 1).

Some syndromes may not present until adulthood, for example, Klinefelter syndrome may present with a primary infertility evaluation. In these cases, the family medicine physician needs to be prepared to access disease-specific information in order to provide education and emotional support to the newly diagnosed patient, or referral to genetic counseling if available.

Types of Genetic Testing

There are five main classes of genetic testing. These include newborn screening, carrier testing, prenatal testing, diagnostic testing, and predictive testing.

The most widespread form of genetic testing currently in use is newborn screening. These tests are done by tandem mass spectroscopy on a state level to screen for numerous genetic disorders at birth, which allows for early detection and intervention to prevent or minimize disease onset or severity [11].

Carrier testing is done to identify individuals who may carry mutations for specific recessive disorders. These tests are appropriate for those with a family history of a specific genetic disorder, or those from an ethnic group with an increased carrier frequency. The carrier status of an individual or couple is important for reproductive decision-making with regard to their risk of having a child affected with the disorder. In order to pass on the disease, both parents must be carriers of the recessive disorder, and then each pregnancy will have a 25% chance of inheriting both mutations and developing the disorder. One prevalent carrier testing program is for Tay-Sachs disease among people of Ashkenazi Jewish descent where the carrier frequency is 1/27 [12]. Other examples include cystic fibrosis and sickle cell disease.

Pregnancy-related testing includes preconception testing, preimplantation testing, and prenatal testing. Preconception testing is a form of carrier testing done prior to conception. Preimplantation genetic testing is done on embryos generated by IVF for selection and implantation to avoid embryos that are homozygous for a specific genetic condition. Prenatal testing is done to identify genetic changes in the developing fetus when there is a higher risk of genetic or chromosomal disorders due to advanced maternal age or strong family history of a particular condition. These tests are typically performed on cells obtained from amniocentesis or by chorionic villus sampling.

Diagnostic genetic testing is used to confirm a suspected genetic diagnosis in an already affected individual. This type of testing provides a yes or no answer and can diagnose or rule out a specific

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Table 1 Common genetic disorders in primary care

Disorder	Inheritance
Achondroplasia	Autosomal dominant
Adult polycystic kidney disease	Autosomal dominant and autosomal recessive
Alpha 1 antitrypsin deficiency	Autosomal codominant
Congenital adrenal hyperplasia	Autosomal recessive
Cystic fibrosis	Autosomal recessive
Down syndrome	Spontaneous chromosomal abnormality
Familial hypercholesterolemia	Autosomal dominant
Fragile X	X-linked dominant
Galactosemia	Autosomal recessive
Gaucher	Autosomal recessive
Hemochromatosis	Autosomal recessive
Hemoglobinopathies	Variable/autosomal recessive/ X-linked
Huntington's chorea	Autosomal dominant
Klinefelter syndrome	Spontaneous chromosomal abnormality
Marfan syndrome	Autosomal dominant
Multiple exostosis	Autosomal dominant
Myotonic dystrophy	Autosomal dominant
Neurofibromatosis	Autosomal dominant
Phenylketonuria	Autosomal recessive
Spinal muscular atrophy	Autosomal recessive
Tay-Sachs	Autosomal recessive
Trisomy 18	Spontaneous chromosomal abnormality
Turner syndrome	Spontaneous chromosomal abnormality

condition as the cause of symptoms. Having a confirmed diagnosis can then help provide anticipatory guidance for the patient in terms of progression and management of their disease.

Predictive testing is used to identify high-risk individuals based on family history, prior to the onset of disease. "Presymptomatic testing" identifies individuals who will go on to demonstrate diseases such as Huntington's chorea. "Predispositional testing" shows that an individual is at higher risk for the development of a certain disease but may not ever develop the disease in one's lifetime, such as breast cancer. The ultimate goal of predictive testing is to prevent or minimize the effects of a genetic disease [7].

Clinical Testing

There are three main types of clinical genetic testing: cytogenetic, molecular, and biochemical testing.

Cytogenetic testing is the examination of whole chromosomes for abnormalities. Whole cells are prepared, and the chromosomes are fixed and stained on slides for analysis. The distinct banding pattern of each chromosome allows for detection of variation. In addition, fluorescent in situ hybridization (FISH) can be used to paint chromosomes or portions of chromosomes with fluorescent molecules to enhance the identification of abnormalities [7].

Biochemical testing uses techniques to evaluate protein activity to assess gene function. These tests measure protein activity and quantity in the collected cell samples. The most prominent example of this is the use of tandem mass spectroscopy in newborn screening [7].

Molecular testing evaluates for DNA sequence changes. Many screening panels have been developed for the most common mutations associated with specific diseases. For example, the CFTR panel screens for the 30 most common mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR). To further enhance detection, additional techniques such as comparative genomic hybridization (CGH), chromosomal microarray analysis (CMA), and DNA chip analysis are utilized to screen and identify small deletions, duplications, or variations in gene expression when compared to a normal-reference DNA [7].

Direct-to-Consumer Testing

In the last several years, a new industry has blossomed as a result of genetic testing advances in the form of direct-to-consumer testing. In this form of testing, test kits are marketed directly to the patient. This type of free-market medical testing is the center of significant debate regarding the appropriateness of medical data being obtained in the absence of physician interpretation, versus the rights of patients to obtain and manage their own

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private medical data. Although most direct-to-consumer testing is paid "out of pocket," some are attempting to work with the insurance industry to achieve third-party billing for these services. In addition, the FDA is now investigating how direct-to-consumer (DTC) testing should be monitored and approved, as this form of medical industry sets a new precedent. There are currently over 400 companies offering DTC genetic testing on the market [13, 14]. They offer a range of services from ancestral DNA analysis to whole genome chip analysis. It is projected that the global market for this technology will reach $3.4 billion by 2024 [13, 14]. The primary concerns at this time are whether the test results oversimplify complex information, mislead patients by not providing complete informed consent, and whether testing meets clinical validity standards [15]. There is further concern as to whether patients can adequately understand the results and the overall implications of the results on their personal health and that of their family. Patients might overestimate their risk of disease which could cause unnecessary stress, or may misinterpret the results resulting in inappropriately increased screening and/or intervention without the context of a knowledgeable physician or other professional directing their care [15]. Nonetheless, DTC testing may provide an excellent opportunity for collaboration between the primary care physician and the patient when it comes to the interpretation of results and integration of the data into personalized medical management. Recently, the FDA has come out with a statement regarding the requirement of repeating the test in a clinical setting prior to utilization of the report for medical decision-making [16].

Result Interpretation

Before ordering any test in medicine, it is critical to understand the potential results one might receive and the potential impact of these results on both medical decision-making and the psychological and social implications for the patient. Testing should generally be reserved for cases in which the result can lead to changes in care that impact clinical outcomes. It is no different when it comes to genetic testing. Genetic testing results can come back as positive, negative, true negative, uninformative negative (see below), false negative, a variant of unknown significance, or a benign polymorphism. The primary care provider must be able to understand the implications of each of these answers and communicate the results with respect to the genetic question at hand.

A positive result means that a mutation or variation was identified. Depending on the context, this can have several different meanings. For simplicity, this will be discussed in the context of carrier testing vs diagnostic testing. If one is testing to determine carrier status, then a positive result confirms that the individual being tested carries an altered form of that gene. If the variation is associated with a recessive disorder, then this person can potentially pass this mutation on to their children, and if the offspring inherits a second mutated copy from the other, parent would manifest the recessive disorder. If the alteration is a marker representing an increased risk for disease, then the presence of the variation would confirm that the individual is at an increased risk for developing that disease in the future.

If testing is being done to confirm a diagnosis associated with a specific mutation, then a positive test result confirms the diagnosis of that disease and may influence disease treatment.

A negative test result means that a mutation or variation was not identified. If testing carrier status in a family with a known mutation, then this result shows that the tested family member did not inherit that specific mutation and is not at higher risk for the disease or syndrome being tested. This is known as a true negative, and it reduces the risk of a specific disease to that of the general population. If the test is being done in the context of a family with a disease or syndrome with no known associated mutation, then a negative genetic screening test result is an uninformative negative. The uninformative negative does not provide clinically useful data, since it does not distinguish between the absence of the mutation or mutations in the individual and the failure to detect the presumed mutation or mutations leading to the condition of interest. A variant of unknown

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significance (VUS) is a new mutation found in the tested individual that has not been previously proven or linked with a specific disease and uncertainty exists whether or not it is related to the disorder in question. It is hoped that in the future research will reclassify variants of unknown significance as a disease associated mutation, a benign polymorphism, or normal variation within the general population.

Pharmacogenomics

With the rapid advances and decreased costs of genomic testing, the implementation of pharmacogenomics (PGx) as standard of practice in primary care is quickly becoming a reality. Currently there are already FDA prescribing guidelines that include PGx recommendations for nearly 400 medications [17]. Many of these medications represent common medications among the prescribing habits of primary care providers [18–22]. It is imperative that primary care providers become familiar with PGx concepts and the resources available to guide practice management decisions to successfully integrate this technology to improve the health and outcomes of patients.

PGx is the study of how genetic variations impact the inte-individual variability of drug response through pharmacokinetics (metabolism and transport) and pharmacodynamics (receptor targets, signaling cascade) [23]. Genetic variation accounts for 20–95% of the differences observed in a patient's response to medication [24]. With the advances in PGx, the expectation is providers can better predict medication response [23], allowing for tailored prescribing for individual patients as opposed to the classic "one size fits all" model.

In addition to improved medication response, a major contribution from PGx is to reduce adverse drug reactions (ADRs). ADRs have a significant impact on rates of morbidity and mortality with an estimated 100,000 deaths/year [25], hospital admissions, and immense impact on health-care costs [26–30]. ADRs have been reported in nearly 10% of patients in the ambulatory primary care setting [31]. More than half of the drugs with frequently reported ADRs are metabolized by cytochrome p450 drug metabolizing family of enzymes (CYP450) [32, 33]. Some of these drug metabolizing enzymes are highly polymorphic, commonly harboring genetic variations called single-nucleotide polymorphisms (SNPs) which can result in a range of metabolic activity [32]. Identification of these genetic variants in patients allows for informed prescribing of medication and dosage to increase the likelihood of drug efficacy and reduce the likelihood of ADRs [20].

CYP450

Enzymes produced from the CYP450 genes are involved in the metabolism of various molecules and chemicals within cells. There are approximately 60 CYP450 genes in humans. A subset of these genes encodes the enzymes needed for 70–80% of all drug metabolisms. CYP450 enzymes are primarily found in liver cells but are also located in other cells throughout the body. Common variations (SNPs and copy number variants) in CYP450 genes can affect the amount or function of the enzymes they encode and therefore how they activate or breakdown medications. These variations can lead to either rapid, normal, or slow metabolism of a drug. If a CYP450 enzyme metabolizes a drug slowly, the drug will remain in its parent form longer. If this drug is active, less of the drug is needed to get the desired effect. A drug that is metabolized more quickly is broken down faster, and therefore a higher dose may be needed to be effective. If the drug is a prodrug, a parent drug molecule that is inactive on its own, it needs to be metabolized to produce a therapeutic effect. In this situation, the potential clinical impact of reduced or enhanced metabolism is reversed [34]. In the case of two of the common CYP genes, *CYP2C9*, and *CYP2C19*, the common polymorphisms give rise to five distinct phenotypes (see Table 1).

PGx Guidelines

Two organizations in addition to the FDA have been established to help evaluate the emerging

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evidence of PGx linkages and publish evidence-based prescribing recommendations to inform clinical practice. FDA PGx information can be found in drug product labeling describing information on drug exposure and clinical response variability, risk for adverse events, genotype-specific dosing, mechanisms of drug action, polymorphic drug target genes, as well as some specific actions to be taken based on the genomic information. In some cases, PGx statements have reached the highest-level FDA warning, a "boxed warning," and recommendations regarding prescribing of affected medications are offered. A complete list of drugs and their labeling information can be found at the FDA website [35].

The Pharmacogenomic Knowledge Base (PharmGKB; [36]) was created in 2000. This NIH-funded project collects, curates, and disseminates scientific knowledge about the impact of human genetic variation on drug responses. Its clinical-focused subgroup, the Clinical Pharmacogenomics Implementation Consortium (CPIC), was formed in 2009, with the goal to accelerate clinical translation of pharmacogenomic data [37]. CPIC creates peer-reviewed and evidence-based gene/drug clinical practice guidelines for those seeking to adopt PGx testing in clinical practice (see example in Table 1). Published guidelines are freely accessible on their website [38]. The CPIC guidelines include a system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, and provide standardized prescribing recommendations based on the genotype/phenotype. Currently, both databases are in a human readable format. The next step is then translating these guidelines into local drug use policies that can be combined with discrete genetic results in the EHR to provide real-time clinical decision support (CDS) to inform treatment decisions at the point-of-care.

Common Clinical Examples

There are many clinically relevant drugs used in the primary care setting that are impacted by PGx. Some of the most well-understood examples at this time include clopidogrel, simvastatin, warfarin, and citalopram as well as the large class of drugs metabolized by *CYP2D6*.

The antiplatelet medication clopidogrel (Plavix®) is a prodrug that requires metabolism to its active form. *CYP2C19* reduced or no function alleles are associated with poor bioactivation of the prodrug, decreased platelet inhibition, and an increased risk of adverse cardiovascular events [39, 40].

CYP2D6 is responsible for metabolizing at least 25% of commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, beta adrenergic blocking agents, antiarrhythmics, and antiemetics. *CYP2D6* poor metabolizers may have toxic levels of the parent drug or failed drug bioactivation such as conversion of codeine to morphine.

Warfarin (Coumadin®) metabolism is an example of how the combined effect from two or more different gene variants can result in changes in both drug pharmacokinetics and pharmacodynamics [41]. Variants identified in *CYP2C9 and CYP4F2* which are responsible for warfarin metabolism [42–45] and *VKORC1* which encodes an enzyme which is needed for effective clotting that is inhibited by warfarin [46], among others, have been shown in combination to explain as much as 35–50% of variation in warfarin drug response [47].

Simvastatin (Zocor®)-induced myopathy has been shown to be associated with variation in the *SLCO1B1* gene which encodes a transporter involved in its hepatic uptake. As high as a 4.5-fold higher odds of myopathy was observed in patients receiving high dose (80 mg) simvastatin who carry just a single at-risk variant [48], resulting in a recommendation for alternative statin or low-dose therapy with simvastatin (20 mg) [49].

PGx Testing

There are currently multiple types of genomic testing technologies on the market. One of the most common and currently least expensive methodologies is a SNP chip array. The SNP chip array

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uses DNA amplification and fragmented genetic target sequences affixed to fluorescent probes to rapidly determine the DNA sequence at specific sites within the genome. In contrast, DNA sequencing reads every DNA base in a targeted region. Next-generation sequencing (NGS) is a newer technology that has dramatically lowered the cost of whole exome sequencing (WES)-coding regions only and even whole genome sequencing (WGS)-coding and noncoding regions. The benefit of chip array is the rapidity of testing, whereas WGS/WES will provide more comprehensive results.

There is an active debate currently in the field as to whether preemptive pharmacogenomic testing versus reactive genotyping is the best method. Because PGx testing is a lifelong result, proponents of preemptive testing argue that given the high incident exposure to medications for which there are PGx recommendations, it will likely be cost-effective to have testing done once in advance of clinical need and for these results to be stored for long-term future use [50]. Prescribing providers can then access gene-drug-specific associations to inform prescribing at the relevant time [51, 52]. One study found that an analysis of over 10,000 patients, preemptive testing revealed a PGx variant in 91% of patients and that 40% of those patients were exposed to at least one of the associated medications in the 3 years following the study [53]. Having this data readily available in the EHR would allow for real time point-of-care prescribing modifications. In addition, the low cost of the large pharmacogenomic panels makes this form of testing less expensive than individual gene testing one at a time [52–54].

Clinical PGx Implementation and a Path Forward

If patients bring genomic test results to the office, providers should assess the source of the test (whether it was an FDA-approved test or if the testing was done in a CLIA lab) and critically review the test information. Specifically, what variants the test assayed and, importantly, what was not tested prior to interpreting results. Further, any clinical recommendations regarding drug therapy should be reconciled with current guidelines such as those provided by CPIC and FDA prior to integrating results into the patient's personal treatment plans. Currently, a recommendation would be to scan and document clinical genomic test results into the EHR in the problem list and black box warnings as allergies, as there is often not yet an existing mechanism to directly import this data. Data from direct to consumer testing must be repeated in a clinical testing lab to validate results prior to use in clinical decision-making.

Table 2: "Poor metabolizer" (PM) refers to combination of no function and/or decreased function alleles; "intermediate" metabolizers" (IM) carry

Table 2 Example CPIC table for antiplatelet therapy recommendations based on CYP2C19 genotype for acute coronary syndrome/percutaneous coronary intervention patients [40, 38]

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations	Classification of recommendations
Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and Normal metabolizer (NM)[a] (*1/*1)	Normal (EM) or increased (UM) platelet inhibition; normal (NM) or decreased (UM) residual platelet aggregation	Clopidogrel: label-recommended dosage and administration	Strong
Intermediate metabolizer (*1/*2, *1/*3, *2/*17)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Moderate
Poor metabolizer (*2/*2, *2/*3, *3/*3)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor	Strong

[a]Updated nomenclature used (normal metabolizer in place of extensive metabolizer)

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combinations of normal function, decreased function, and/or no function alleles, resulting in decreased enzyme activity; "normal metabolizer" (NM) refers to the "normal" phenotype, usually representing the major proportion of the population; "rapid" metabolizers (RM) have increased enzyme activity through combinations of normal and increased function alleles; and finally, the "ultrarapid" metabolizer (UM) phenotype originates from two increased function alleles or more than two normal function alleles (copy number variation) [55]

Cancer Genetics

Cancer Genetic Risk Assessment

In a recessive or simple "two hit" model of cancer development, one must have a cancer causing mutation on each chromosome in specific genes to develop cancer. However, 5–10% of all cancers are related to an inherited cancer syndrome in which individuals inherit one cancer predisposing mutation in all cells of their body and thus only need to acquire one additional cancer causing "hit" to develop cancer in their lifetime (such as exposure to a mutagenic chemical or virus). However, individuals without this inherited cancer-causing predisposition must acquire both hits in their lifetime to develop cancer. There also exist dominant forms of cancer syndromes in which only a single inherited mutation is adequate for the development of cancer. However, due to variable expression or incomplete penetrance, not all patients with dominant cancer mutations will manifest cancer in their lifetime. More than 50 types of hereditary cancer syndromes have been identified, and most are in genes that control cell growth or repair DNA damage. Family Physicians should be able to recognize the "red flags" that are suggestive of an inherited cancer syndrome and properly counsel patients regarding their risk and options for genetic testing and subsequent screening or treatment to mitigate the potential development of cancer [56]. Some cancers can appear to have an inherited pattern in a pedigree but are caused by nongenetic factors such as living environment, tobacco, diet, or other carcinogen exposures.

Specific red flags within a pedigree include similar types of cancer appearing in multiple generations of the same side of the pedigree, affected individuals younger than 50, male breast cancer, bilateral breast cancer, and cancer diagnosed at an unusually young age. Other red flags include multiple different cancer types occurring independently in the same person, several close relatives with the same type of cancer, the presence of birth defects that are known to be associated with certain inherited cancer syndromes or being from an ethnic group with a high frequency of certain cancer syndromes. To date more than 50 hereditary cancer syndromes have been identified (see Table 3).

If a specific syndrome is suspected, genetic testing can be done to confirm the presence of a mutation. Most experts agree that testing should be recommended if there is a personal or strong family history of an inherited cancer condition and if the test can be adequately interpreted, and the results provide information that will guide medical decision-making. Once this mutation is identified, it can be looked for in relatives of the index case.

Genetic Risk Reduction

Once testing for a potentially deleterious mutation has been confirmed, the patient may be able to take steps to reduce the risk of developing cancer or to begin early or intensive screening for detection. Clinical guidelines include screening at an earlier age for cancer, medication, and prophylactic surgery such as a mastectomy and/or oophorectomy with hereditary breast and ovarian cancer syndrome or colectomy for Lynch syndrome [57]. Other forms of risk reduction might include modifying personal behaviors such as smoking, weight reduction, and abstinence from alcohol.

Epigenetics

Epigenetics is the study of factors that control gene expression, rather than analysis of the DNA code itself [58]. These factors are able to turn gene expression on or off. Epigenetic factors are what help to distinguish cell types in different organs that share all of the same DNA complement, and

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Table 3 Common cancer genetic syndromes

Syndrome	Genes	Related cancer types
Hereditary breast cancer and ovarian cancer syndrome	BRCA1, BRCA2	Female breast, ovarian, and other cancers, including prostate, pancreatic, and male breast cancer
Li-Fraumeni syndrome	TP53	Breast cancer, soft tissue sarcoma, osteosarcoma (bone cancer), leukemia, brain tumors, adrenocortical carcinoma (cancer of the adrenal glands), and other cancers
Cowden syndrome (PTEN hamartoma tumor syndrome)	PTEN	Breast, thyroid, endometrial (uterine lining), and other cancers
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	MSH2, MLH1, MSH6, PMS2, EPCAM	Colorectal, endometrial, ovarian, renal pelvis, pancreatic, small intestine, liver and biliary tract, stomach, brain, and breast cancers
Familial adenomatous polyposis	APC	Colorectal cancer, multiple nonmalignant colon polyps, and both noncancerous (benign) and cancerous tumors in the small intestine, brain, stomach, bone, skin, and other tissues
Retinoblastoma	RB1	Eye cancer (cancer of the retina), pinealoma (cancer of the pineal gland), osteosarcoma, melanoma, and soft tissue sarcoma
Multiple endocrine neoplasia type 1 (Wermer syndrome)	MEN1	Pancreatic endocrine tumors and (usually benign) parathyroid and pituitary gland tumors
Multiple endocrine neoplasia type 2	RET	Medullary thyroid cancer and pheochromocytoma (benign adrenal gland tumor)
Von Hippel-Lindau syndrome	VHL	Kidney cancer and multiple noncancerous tumors, including pheochromocytoma

this is why genetically identical twins are not fully phenotypically identical [58]. This epigenetic modification can be part of normal cellular processes, such as X-inactivation [59].

There are three main methods of epigenetic modulation with interact with each other to modify gene expression, including DNA methylation, histone modification, and RNA-associated silencing [59]. Interaction with the environment including naturally occurring and man-made compounds can modify these epigenetic signals. Therefore, epigenetics can be considered the interface between the environment and the genome [6]. Therefore, environmental factors may play a large role in the disruption in gene expression leading to over or under expression of proteins, both of which can result in phenotypic changes, including disease.

Counseling Considerations

Any person considering genetic testing should be counseled by a trained professional. These may include physicians, genetic counselors, or other health-care providers with additional training in genetic risk assessment and counseling. The counseling should focus on the process of informed consent including the risks, benefits, and limitations of genetic testing in the context of the disease being tested for. Pretest counseling should include which specific tests are most appropriate, the accuracy of the test, the medical implications of a positive or negative result, or of an uninformative result. In addition, the psychosocial implication of genetic test results on the individual being tested as well as relatives who may be implicated by the result and the potential for future inheritance should be considered [60]. Finally, additional discussions regarding confidentiality and insurance discrimination should be addressed. Written informed consent should then be obtained. Though the process of detailed family history taking, it may be determined that testing is not indicated, or that a different family member is the one who should be considered for testing first. Testing should then be followed up by posttest counseling to review the results and develop a management plan accordingly as well as again assessing the

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psychosocial impact of these results [61]. If at any point in this process, the family medicine physician feels that they have exceeded their knowledge or comfort level regarding the condition or conditions, or if the condition involves multiple complex tests, then referral to a genetic counselor or specialist might be considered [61].

In the specific case of pediatric diagnosis, physicians should be prepared to provide education on the etiology, prognosis, genetic mechanism, and recurrence risk of the disorder as well as available treatment options. These children can often be successfully managed between the primary care physician and genetic specialist [5, 62, 63].

Ethics and Privacy Laws

As with many aspects of primary care medicine, genetic medicine frequently encounters sensitive and ethical issues including consanguinity, ethnicity, and patient confidentiality. The potential impact for harm if genetic information were shared without regard is enormous. In addition, the information is not unique to the individual being tested but could possibly impact multiple generations of relatives.

While genetic test results are governed under the same HIPPA laws as all other protected health information, they are not always private. For example, health insurance companies will have access to these results. Genetic privacy and nondiscrimination is therefore of utmost importance. Legal protection in the form the Genetic Information Nondiscrimination Act (GINA) was instituted in 2008 in the United States to protect such information and to prevent discrimination based on genetic test results [13, 64, 65]. GINA prohibits genetic information from being used in health insurance eligibility or to establish premiums or to prevent employment. GINA is not all encompassing and currently does not apply to members of the military and does not apply to other insurance coverage such as life insurance, disability insurance, or long-term care insurance. There are additional laws that vary by state, which may cover these gaps.

The Future of Genetics in Primary Care

It is likely that, in the near future, Family Physicians will be utilizing genetic tools to identify and prevent many common illnesses such as diabetes, hypertension, Alzheimer's, and chronic obstructive pulmonary disease. How soon this technology becomes integrated into every day practice remains to be seen. In the meantime, it is clear that the Family Physician will need to continue to advance their understanding of the field of genetics and personalized medicine and participate in developing methods of effectively incorporating the technology into daily practice.

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Problems of the Newborn and Infant 16

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Newborn Resuscitation

Term infants who appear well at delivery, have clear amniotic fluid, and good respiratory effort and muscle tone should receive routine newborn care. This includes providing warmth, clearing of the airway as needed, and drying and stimulating of the infant. Ongoing assessment of airway, breathing, circulation, and color should occur as the newborn transitions to extrauterine life. The initial three questions a provider should consider are (1) is this a term newborn, (2) is the tone good, and (3) is breathing or crying present. If the answer is yes to all of these, the infant may remain with the mother for routine care. This initial assessment may occur while the newborn is skin to skin with the mother, during which time any gross abnormalities can generally be observed and ongoing observation by trained staff maintained [1, 2].

If the answer is no to any of the three abovementioned questions, the newborn should be transferred to a radiant warmer to receive one or more of the following interventions in sequence: initial stabilization, ventilation with or without supplemental oxygen, initiation of chest compressions, and administration of epinephrine or volume. All health-care staff involved in the delivery of newborns should be skilled in neonatal resuscitation [1, 2].

The delivery suite should contain equipment appropriately sized to resuscitate newborns of all gestational ages and sizes. This includes a radiant warmer, a source of oxygen with an oxygen blender, instruments for intubation and other airway equipment for suctioning and ventilating, trays for possible umbilical line placement or establishing intravenous access, and drugs such as epinephrine [2].

The initial steps of newborn resuscitation are to maintain normal temperature of the infant by drying well and placing either skin to skin with mother or under a radiant heat source, positioning the infant in a neutral "sniffing" position to open the airway, suctioning the mouth and nose of secretions with a bulb syringe or suction catheter, and providing positive pressure ventilation for newborns with heart rates less than 100 beats/min and apnea or irregular breathing. Most infants respond to these efforts, but if not, further measures include repositioning techniques to overcome mechanical impediments. If the heart rate remains less than 60 beats/min despite intubation and 30 s of effective positive pressure

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ventilation, chest compressions should be initiated. Central access should be obtained via umbilical vessels and emergency drugs administered [1, 2].

Stabilization for Transfer to Higher Level of Care

Once spontaneous circulation returns, treatment involves management of multiorgan dysfunction and provision of a higher level of care in a neonatal intensive care unit (NICU). This may require transport to a tertiary care center. Effective communication with and support of the family should begin early. Goals of management include maintaining adequate ventilation, blood pressure, cerebral perfusion, and cardiac function.

Giving Bad News to Parents After Delivery

One of the most difficult duties of the physician is breaking bad news. The way in which bad news is delivered has a significant impact on the family's grieving process. The physician should provide information in accordance with the patient's needs and desires; assess the recipients' ability to comprehend; determine the family's expectations and readiness to hear the bad news; support the family by employing skills to reduce the emotional impact; and develop a strategy in the form of a plan to move forward. The physician should always be sensitive to the reaction of patients and their families [3].

Common Problems in the Nursery

Respiratory Distress

Respiratory distress may be a transient finding in newborns manifested by tachypnea, grunting, nasal flaring, retractions, and cyanosis. Transient tachypnea of the newborn (TTN) presents within the first hours after birth and shows gradual improvement with most symptoms resolving within 24 h, although TTN may last up to 72 h. Supplemental oxygen may be required. Chest radiographs (CXR) show perihilar streakiness and fluid in the fissures. Persistent or worsening symptoms should prompt an investigation for neonatal sepsis [2].

Respiratory distress syndrome (RDS) due to surfactant deficiency and an inability to maintain alveolar stability is more common in premature newborns or infants born to diabetic mothers. Classic CXR findings include a "ground glass" appearance with air bronchograms. Hypoxia and hypercarbia may be present. The use of antenatal steroids and surfactant administration have decreased the incidence and severity of RDS.

Persistent, severe, or worsening respiratory symptoms, regardless of etiology, should prompt transfer to a higher level of care. Pneumonia, pneumothorax, persistent pulmonary hypertension, and diaphragmatic hernia should be considered in the differential diagnosis of respiratory distress in the newborn.

Late Preterm Infants

Late preterm infants are born at a gestational age between 34 and 36 6/7 weeks. Infants in these gestational ages have increased over recent years, now accounting for more than 70% of all preterm births. Reasons for this increase include a significant increase in inductions of labor and cesarean deliveries and increases in multiple births. Compared to term infants, late preterm infants have higher morbidity and mortality, including a higher prevalence of respiratory distress, temperature instability, hypoglycemia, kernicterus, apnea, seizures, feeding problems, and rehospitalization after discharge. Feeding problems include preterm infants being much more likely than full-term infants to require supplemental intravenous fluids or gavage feeding. Late preterm babies have at least four times the risk of hyperbilirubinemia, compared to term infants. Discharge of late preterm newborns should be delayed until they have demonstrated reliable and appropriate intake with weight gain and absence of hypothermia, hypoglycemia, or

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apnea, and close outpatient follow-up is in place [2].

Small for Gestational Age

Small for gestational age (SGA) newborns are defined by a birth weight (BW) below the tenth percentile for gestational age. SGA newborns may result from constitutional factors such as maternal height, weight, ethnicity, and parity but will eventually reach their appropriate growth potential.

Infants with intrauterine growth restriction are classified as "symmetric" or "asymmetric." Symmetric growth restriction starts early in gestation and results from pathology that might include congenital infections, chromosomal abnormalities, or decreased nutrient supply. The entire body is proportionately small, including weight, length, and head circumference. Asymmetric growth restriction implies a fetus who is undernourished, beginning later in gestation, directing most of its energy to maintain growth of vital organs at the expense of liver, muscle, and fat. In this case, the newborn has relatively normal length and head circumference but reduced body weight, small abdominal circumference, scrawny limbs, and thinned skin [4]. Regardless of etiology, SGA newborns experience increased risks of negative outcomes including hypothermia and hypoglycemia.

Large for Gestational Age

Infants who are born large for gestational age (LGA) have a birth weight greater than the 90th percentile for gestational age. Macrosomia refers to excessive intrauterine growth beyond a specific threshold regardless of gestational age. There is a significant increase in morbidity among neonates above a weight of 4500 g.

The excessive fetal growth appears to result from increased delivery of nutrients to the fetus due to genetic and intrauterine environmental factors. Genetic factors include syndromes and familial traits by which mothers who were LGA are more likely to deliver an LGA infant than mothers who were appropriate for gestational age. Intrauterine environmental factors include maternal obesity, diabetes, or excess gestational weight gain. Complications of LGA infants include increased birth injury such as brachial plexus or clavicular fracture, respiratory distress, hypoglycemia, polycythemia, and perinatal asphyxia [2].

Neonatal Sepsis

Neonatal sepsis occurs in approximately 1–2 cases/1000 births. It is divided into early-onset (<7 days of age) and late-onset sepsis (>7 days of age). Early-onset sepsis tends to occur early, often on the first day of life, with the majority of cases presenting by 12 h of age. Respiratory distress due to pneumonia is the most common presenting sign, but other findings may include low Apgar scores, poor perfusion, or hypotension. Late-onset (7–90 days) sepsis may present in a more subtle manner with poor feeding, lethargy, hypotonia, temperature instability, new or increased oxygen requirement, or apnea. It is associated more commonly with meningitis or other localized infections [5, 6].

The risk of early-onset infection increases if rupture of the maternal membranes occurs more than 24 h prior to delivery and even more significantly with chorioamnionitis. The organisms that most commonly cause early-onset infection include group B streptococcus (GBS, or *Streptococcus agalactiae*), Gram-negative enteric pathogens such as *Escherichia coli*, and *Listeria monocytogenes*. Late-onset sepsis may be caused by these organisms, as well as non-typeable *Haemophilus influenzae*, enterococci, *Staphylococcus aureus*, and coagulase-negative staphylococci [5].

Maternal risk factors for neonatal sepsis include GBS colonization at the time of delivery, chorioamnionitis, intrapartum maternal temperature ≥38 °C, delivery at <37 weeks gestation, and membrane rupture ≥18 h. GBS screening is recommended between 36 and 38 weeks of gestational age via vaginorectal swab culture. Alternatively, nucleic acid amplification testing may be

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performed at the time of delivery if screening was not obtained earlier. Standard GBS screening may have low sensitivity, so the provider should maintain a high index of suspicion for this condition. Intrapartum antibiotic prophylaxis with penicillin G, or ampicillin or cefazolin as alternatives, given intravenously ≥4 h prior to delivery has been shown to be effective in decreasing the incidence of early-onset neonatal sepsis, but not late-onset GBS disease. In cases of penicillin allergy, clindamycin or vancomycin may be used [7].

The clinical diagnosis is difficult because the signs of sepsis are nonspecific and can be seen in other conditions not related to infection [6].

Symptomatic neonates should undergo a full diagnostic evaluation and receive empiric antibiotics. Full evaluation includes complete blood count (CBC) with differential, blood culture, lumbar puncture if clinically stable, and CXR (if respiratory symptoms are present). As appropriate, cultures from tracheal aspirates, C-reactive protein (CRP), and procalcitonin should be obtained. The Centers for Disease Control and Prevention has developed a mobile application to aid in point-of-care evaluation and management for newborn sepsis [8].

Infants being evaluated for late-onset sepsis should receive the studies described for early-onset sepsis, as well as urine cultures and cultures from any other potential foci of infection.

Treatment of infants with presumed early-onset sepsis should include broad-spectrum coverage including ampicillin, plus an aminoglycoside or third-generation cephalosporin such as cefotaxime or ceftazidime. Late-onset sepsis empiric therapy involves coverage for the same organisms for early-onset disease, with the addition of coverage for staphylococci, such as with vancomycin. Initial broad-spectrum coverage should also include cefotaxime or ceftazidime or an aminoglycoside. The blood cultures, inflammatory markers, and clinical course will guide the duration of antibiotic therapy. If cultures are negative after 48 h, antibiotics may be discontinued [5, 6]. Concern for herpes infection should prompt empiric initiation of intravenous acyclovir and appropriate evaluation.

Neonatal Jaundice

Bilirubin is a potent antioxidant and peroxyl scavenger which may be protective against oxygen toxicity in the first days of life for the newborn. Normal homeostasis allows for a balance of bilirubin production, conjugation, and elimination. An immature liver and increased hemolysis in the newborn are factors contributing to increased levels of bilirubin. Jaundice refers to yellow discoloration of the skin, mucous membranes, and sclera, usually associated with total serum bilirubin >5 mg/dL in the newborn period. Although generally benign and transient, hyperbilirubinemia, or excess bilirubin in the blood, can cause severe neurological sequelae by accumulation of toxic amounts of unconjugated bilirubin in the brain leading to kernicterus [9, 10].

In the first week of life, a slight increase in unconjugated bilirubin, derived from normal hemolysis of red blood cells (RBCs) and predominantly bound to albumin, is a normal physiologic process and usually does not merit treatment. Evidence-based guidelines exist to determine levels at which intervention should be considered. Jaundice may be pathologic if presenting within the first 24 h of life [9, 10]. Breastfeeding-associated jaundice, in which breast milk consumption is inadequate, can contribute to early onset of jaundice. In this condition, the lack of adequate intake is the primary contributing factor [10–12]. Interventions to improve breast milk transfer from mother to infant should be undertaken.

Elevated bilirubin may also result from increased hemolysis, decreased conjugation of bilirubin in the liver, decreased excretion of bilirubin, or liver cellular damage. Pathologic forms of hemolysis include ABO incompatibility, Rh isoimmunization, RBC enzyme deficiencies, RBC membrane abnormalities, hemoglobinopathies, or polycythemia. Decreased conjugation of bilirubin may occur due to glucuronyl transferase deficiency disorders like Crigler-Najjar syndrome or Gilbert syndrome. Decreased excretion of bilirubin includes conditions causing abnormal biliary ducts, e.g., extrahepatic biliary atresia, or increased enterohepatic bilirubin recirculation.

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Hepatitis in the newborn may result from congenital infections or inborn errors of metabolism [9, 10].

The principal goal of diagnosis and management of severe hyperbilirubinemia is to prevent acute bilirubin encephalopathy and subsequent kernicterus. Acute encephalopathy results in lethargy, poor feeding, vomiting, high-pitched cry, opisthotonos, seizures, and hypotonia. Kernicterus is an irreversible brain injury characterized by choreoathetoid cerebral palsy, auditory neuropathy, and paralysis of upward gaze [9, 10].

Primary Prevention

Mothers are recommended to initiate breastfeeding within the first hour after birth and continue unrestricted feeding at least 8–12 times a day. Increased frequency of feeding promotes greater excretion of bilirubin in the stool, resulting in decreased hyperbilirubinemia [11, 12].

Secondary Prevention

ABO and Rh (D) blood types and unusual isoimmune antibodies should be tested in all pregnant women. If the maternal blood type is not known, or the mother is either O blood type or Rh factor negative, then ABO, Rh (D), and Coombs testing should be performed on cord blood [10].

Assessment

All jaundiced infants require a full assessment including maternal and family history and clinical examination. This includes screening with transcutaneous bilirubinometry (TcB) or total serum bilirubin (TSB) for all infants, at least prior to discharge. TcB measures bilirubin on the surface of the skin; however, caution must be exercised when used on patients already receiving phototherapy and in newborns with darker colored skin. Any TcB $\geq$75% on the nomogram [10] should have a TSB. Infants with a TcB value $\geq$12 mg/dL, with an onset of jaundice in the first 24 h, or receiving phototherapy should be evaluated only by TSB. Those patients who are undergoing treatment should also only be evaluated with TSB.

Additionally, consideration of maternal and neonatal risk factors must be accounted for which could impact further testing. Maternal risk factors include having a previous baby requiring phototherapy, diabetes, being of Eastern Asian or Mediterranean descent, ABO incompatibility, or a family history of inherited hemolytic disorders. Neonatal risk factors include prematurity, poor oral feeding, hemolytic disease, and birth trauma.

Breast milk jaundice occurs in the second week of life and may take up to 3–4 months to resolve. If there is no evidence of an alternative pathologic etiology, there is no elevation in conjugated bilirubin, and the infant is growing and developing appropriately, no further treatment is needed [12].

Laboratory Assessment

Each bilirubin measurement should be interpreted using the bilirubin nomogram. Using the nomogram to stratify risk helps to identify hyperbilirubinemia requiring treatment [10].

Any infant with jaundice appearing within the first 24 h or with jaundice prolonged in nature should undergo appropriate investigation. These may include a CBC with indices and peripheral smear, reticulocyte count, total and direct bilirubin to evaluate cholestasis, direct antiglobulin or Coombs test, and maternal and infant blood group. Depending on the clinical picture, a serum albumin, sepsis workup, thyroid studies, reducing substances in urine checking for galactosemia, or glucose-6-phosphate dehydrogenase levels may be appropriate.

A direct bilirubin level above 1 mg/dL (when the total bilirubin level is $<$5 mg/dL), or a direct bilirubin level higher than 20% of the total bilirubin level (when TSB is $>$5 mg/dL), constitutes direct (conjugated) hyperbilirubinemia. Direct hyperbilirubinemia is always pathologic and should trigger prompt evaluation.

Treatment

Phototherapy is the most common treatment for most cases of indirect hyperbilirubinemia. It is noninvasive and works by converting unconjugated bilirubin in the skin to a water-soluble form that can be excreted in bile without conjugation. A reduction of 0.5 mg/dL/h in the TSB should be noted when measured 4–6 h after treatment initiation. Overall a decrease in TSB by

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30–40% should occur within the first 24 h. The newborn eyes should be covered with eye patches, and the oral intake should be monitored. Care should be taken to avoid hyper/hypothermia during phototherapy [9, 10].

While most infants with moderate indirect hyperbilirubinemia can be treated effectively with phototherapy, extreme hyperbilirubinemia is a medical emergency, and exchange transfusion should be initiated without delay when bilirubin levels reach treatment thresholds. Exchange transfusion is an invasive procedure involving risks of infection, electrolyte disturbances, thrombocytopenia, fluid overload, coagulopathy, necrotizing enterocolitis (NEC), and thrombosis and should be performed in a neonatal intensive care unit (NICU) [9, 10].

Hypoglycemia

Low blood glucose levels in newborns are a common and usually transient disorder in the neonatal period. Glucose concentration decreases in the immediate postnatal period to as low as 30 mg/dL in many healthy infants at 1–2 h after birth. Glucose levels below 40 mg/dL after the first feeding are considered hypoglycemic. By 3 h, the glucose concentration in normal full-term infants stabilizes at $\geq$45 mg/dL and should be maintained above that threshold unless there is a suspicion for hyperinsulinism, in which case the threshold should be $\geq$65 mg/dL [13, 14].

Certain maternal risk factors, e.g., pre-gestational or gestational diabetes, in addition to medications such as beta-blockers and oral hypoglycemics, increase the risk of neonatal hypoglycemia. Prematurity, intrauterine growth restriction, postmaturity, infection, polycythemia, and hypothermia are also risk factors [13, 14]. Newborns placed skin to skin with their mothers after delivery, and with early initiation of breastfeeding, experience lower rates of hypoglycemia [15]. Hypoglycemic newborns who are asymptomatic may be treated with breastfeeding, with oral feeding with formula or pasteurized donor human milk, or with buccal dextrose gel, while symptomatic infants or those with severe or persistent hypoglycemia may require intravenous glucose support and transfer to a higher level of care.

Metabolic Disorders

Inborn errors of metabolism may present as severe metabolic emergencies resulting in neurologic injury, significant morbidity, and even death. Early recognition, prompt evaluation, and timely management are paramount. Initial symptoms may include vomiting, lethargy, seizures, irregular breathing leading to apnea, and hypothermia. The most common finding in patients subsequently diagnosed as having an inborn error of metabolism is neurologic, followed by gastrointestinal symptoms. After excluding sepsis-like syndromes, or other electrolyte abnormalities such as hypocalcemia, the main metabolic disorders requiring evaluation include urea cycle disorders, fatty acid oxidation defects, and amino acid disorders. All states require newborn screening for certain disorders that are life-threatening or detrimental to long-term health. These disorders are evaluated at an early age because early identification and intervention improve outcomes. Blood is collected by capillary specimen (heel stick) for an initial screen between 24 and 48 h, or before hospital discharge. If the initial screen is collected when the newborn has been feeding orally for less than 24 h, a second screen is required and should be collected between 7 and 14 days of age. State requirements for testing may vary [2]. Most state laboratories offer expanded metabolic screening for a wide variety of metabolic and genetic conditions, and providers should consult their state labs for the most recent information.

Anemia

Anemia is a reduction in RBC number, hematocrit, or hemoglobin concentration to a value >2 standard deviations below the age-specific mean. Anemia in infancy may result from increased erythrocyte destruction, loss of

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RBCs, or inadequate RBC production [16]. The World Health Organization [WHO] [17] recommends delayed umbilical cord clamping (not earlier than 1 min after birth) for improved maternal and infant health and nutrition outcomes, especially iron stores for the newborn. Early cord clamping (less than 1 min after birth) is not recommended unless the neonate is asphyxiated and needs prompt resuscitation. Delayed umbilical cord clamping should not be confused with milking of the cord. The terms are not synonymous. Milking refers to physically expressing blood from the umbilical cord toward the newborn before clamping the cord. Umbilical cord milking in term babies generally is discouraged, as it may increase the risk of polycythemia and hyperbilirubinemia [18].

Initial evaluation of neonatal anemia includes review of perinatal history, physical exam, and assessment of volume status. Labs should include CBC with indices, reticulocyte count, peripheral blood smear, and Coombs test [16]. A Kleihauer-Betke test for fetal cells in the mother's circulation also may be performed. Treatment will be guided by the clinical severity of the anemia and the underlying illness. Transfusions may be required to restore adequate tissue oxygenation and expand circulating blood volume in some cases [16].

Polycythemia

Polycythemia, an abnormal elevation of the circulating RBC mass, is seen frequently in newborns. In newborns, it is defined as a venous hematocrit greater than 65% or a hemoglobin value greater than 22 g/dL, with the normal hematocrit and hemoglobin being 50.3% and 15.9 g/dL, respectively. Although neonatal polycythemia usually represents a normal fetal adaptation to hypoxemia rather than a true hematopoietic defect, the abnormal increase in hematocrit increases the risk of hyperviscosity, microcirculatory hypoperfusion, and multisystem organ dysfunction. Clinical features associated with neonatal polycythemia are generally nonspecific and may include ruddy complexion, irritability, jitteriness, tremors, feeding difficulties, lethargy, apnea, cyanosis, respiratory distress, and seizures. Neurologic signs may also be related to metabolic problems such as hypoglycemia and hypocalcemia [19, 20].

Close attention should be paid to the technique of sample collection while interpreting the test results. Capillary blood samples often show hematocrits that are 5–15% higher than venous samples; therefore, high hematocrit measurements in samples obtained by heel sticks should be confirmed with a free-flowing venous sample.

Polycythemic infants should be evaluated for underlying causes such as intrauterine growth restriction, maternal diabetes, or birth asphyxia. Because clinical manifestations of hyperviscosity can overlap with other conditions, alternative causes for the symptoms should always be carefully excluded. Infants also should be monitored for systemic complications of polycythemia such as thromboses, NEC, hypoglycemia, hypocalcemia, hyperbilirubinemia, and thrombocytopenia. Asymptomatic infants with central hematocrits between 60% and 70% can be monitored closely and aggressively hydrated with adequate enteral intake or intravenous fluids. The hematocrit should be reassessed in 12–24 h, and plasma glucose, TSB, and cardiorespiratory status should be monitored. Patients with polycythemia showing signs or symptoms related to hyperviscosity are frequently treated with plasma exchange therapy. By replacing some of the circulating RBC mass with a crystalloid solution, plasma exchange therapy may reduce blood viscosity and improve end-organ perfusion [19, 20].

Birth Injuries

Birth injuries are defined as a structural destruction or functional deterioration of the body secondary to a traumatic birth. Risk factors include macrosomia and use of instruments, such as forceps or vacuum extraction, during the birth process [21].

Caput succedaneum is a collection of fluid in the superficial scalp that crosses suture lines. It occurs secondary to molding pressure during

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labor and resolves within 4–6 days. Cephalhematoma is a subperiosteal collection of blood that does not cross the suture lines. It is not associated with substantial blood loss and tends to enlarge until about day 3 of life, typically resolving within 3–4 weeks. Subgaleal hemorrhage is a collection of blood between the epicranial aponeurosis and periosteum of the skull. Risk of subgaleal hemorrhage is increased with vacuum-assisted deliveries and can lead to hemorrhagic shock. Clinical findings include tachycardia, a falling hematocrit, and increasing head circumference. Subdural hemorrhage is bleeding between the dura mater and arachnoid layer of the brain that is caused by the rupture of bridging veins. The risk is increased with the use of instruments during delivery. If symptomatic, infants often present with respiratory depression, apnea, and/or seizures.

Facial nerve injury is caused by compression of the facial nerve, often associated with the use of forceps. Most cases resolve within 2–3 weeks. Brachial plexus injuries are the result of damage to the spinal roots C5–T1 that causes paralysis of the upper arm muscles. The most common brachial plexus injury is Erb's palsy, affecting C5 and C6. The arm is adducted with internal rotation, full extension at the elbow, pronation of the forearm, and flexion of the wrist, creating the classic "waiter's tip" posture. The Moro reflex will be asymmetrical. Brachial plexus injuries usually resolve spontaneously, but physical therapy may be considered.

Clavicular fractures are the most common fracture in newborns. Risk factors include macrosomia and shoulder dystocia. It is associated with tactile crepitus over the affected side, with any discomfort resolving within 5–7 days [21].

See Table 1 for an overview of common anomalies encountered in the newborn.

Human Immunodeficiency Virus (HIV) Infection in Newborns and Infants

Effective prevention strategies have reduced the risk of perinatal transmission of HIV infection to less than 1–2% in the United States; however, failures to fully implement these strategies have resulted in vertically transmitted infant HIV infections. All pregnant women should be screened for HIV, and repeat testing at the time of delivery is suggested in high-risk situations or individuals [22, 23].

The predominant route of HIV infection in children is maternal to child transmission including intrauterine, intrapartum, and postnatal, the latter especially through breastfeeding, which is not recommended in the United States, but global recommendations vary. In the absence of anti-retroviral preventive interventions, in nonbreastfeeding populations, 25–30% of infants born to HIV-infected women will become infected. Rates can be as high as 50% for infants with prolonged breastfeeding [22, 23].

In the AIDS Clinical Trials Group 076 trial, zidovudine given during pregnancy, intrapartum, and to the infant after birth was shown to reduce vertical transmission significantly from 26% to 8% in the absence of breastfeeding. Follow-up studies found better efficacy for combination anti-retroviral maternal therapy using at least three drugs from two different classes. This combination therapy has decreased maternal to child transmission to less than 2%. Currently all HIV-exposed infants should receive zidovudine prophylaxis as soon after birth as possible and preferably within 6–12 h of delivery. The usual dose for gestational age $\geq$35 weeks is 4 mg/kg/dose orally twice daily for 6 weeks. Dosing varies for preterm infants (<35 weeks) [22, 23].

Virologic testing (HIV DNA, PCR, or HIV RNA assays) should be performed within the first 14–21 days of life, at age 1–2 months, and then at age 4–6 months for all HIV-exposed infants. Primary care physicians can reference the American Academy of Pediatrics (AAP) Committee on Infectious Diseases [23] guidelines for prevention, evaluation, and management of newborns and infants exposed to HIV. Consultation with a pediatric infectious disease or HIV specialist is recommended whenever possible.

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Table 1 Approaches to common neonatal anomalies

Abnormality	Causes	Evaluation/treatment
Head		
Caput succedaneum	Soft tissue swelling of scalp crossing suture lines, occurs with assisted vaginal birth but may occur with spontaneous vaginal or cesarean delivery	Observation
Cephalhematoma	Subperiosteal hemorrhage, does not cross suture lines. More common with assisted vaginal birth	Observation; treat jaundice if develops
Subgaleal hemorrhage/hematoma	Hemorrhage into subgaleal space	Rapid volume resuscitation; monitoring; rare need for surgical evacuation
Macrocephaly (head size >97%)	May be normal; hydrocephalus; genetic and metabolic disorders	Check for neurologic impairment; consider ultrasonography or head magnetic resonance imaging (MRI)
Microcephaly (head size <3%)	Cerebral dysgenesis; prenatal insults; other syndromes; familial	MRI, maternal phenylalanine level, viral studies
Large fontanels	Skeletal disorders; chromosomal anomalies; hypothyroidism; high intracranial pressure	Check for neurologic impairments; obtain thyroid function tests
Small fontanels	Hyperthyroidism; microcephaly; craniosynostosis	Check for neurologic impairments; consider head imaging
Craniotabes (softening of cranial bones giving a "ping-pong ball" sensation)	Prematurity; if local, benign bone demineralization; if generalized, syphilis or osteogenesis imperfecta	Should recalcify and harden over 3 months. If persists, screen for syphilis and check for blue sclera and fractures
Eyes		
Abnormal red reflex ("white pupil")	50% of patients have cataracts, must rule out retinoblastoma	Ophthalmologic evaluation
Nasolacrimal duct obstruction (6% of newborns; overflow tearing or mucopurulent drainage; erythema)	Incomplete canalization of duct with residual membrane near nasal cavity; 96% resolve spontaneously by 1 year	Nasolacrimal massage tid; topical antibiotics for mucopurulent drainage; surgery at 9–12 months, earlier if severe
Ears		
Any significant ear anomaly and preauricular pits/fistulas		Check for hearing impairment
Mouth/palate		
Long philtrum; thin upper lip; small jaw; large tongue	Fetal alcohol syndrome; other genetic syndromes	Check for genetic abnormalities; maternal alcohol use
Epstein's pearls (2–3 mm white papules on the gums or palate)	Keratogenous cysts	Spontaneous resolution in weeks; reassurance
Short lingual frenulum ("tongue-tie")	Normal	Clip if feeding impaired; tip of tongue notches when extruded or cannot touch upper gums
Cleft lip or palate	Isolated variant; some genetic anomalies	Feeding assessment; lip repair usually at 3 months (exact timing varies per patient, surgeon will advise based on individualized plan), palate by 1 year; revision of repair at 4–5 years; speech therapy

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Table 1 (continued)

Abnormality	Causes	Evaluation/treatment
Neck		
Fistulas, sinuses, or cysts midline or anterior to the sternocleidomastoid (SCM); may retract with swallow	Branchial cleft anomalies; thyroglossal duct cysts	Nonemergent surgical referral
Cystic hygroma (soft mass of variable size in the neck or axilla)	Dilated lymphatic spaces (failure of drainage into jugular vein)	Semiurgent surgical referral as lesion can expand rapidly; consider karyotype
Congenital torticollis (tilting of the infant's head due to SCM spasm)	Usually an isolated neurologic defect from traumatic delivery; appears at 2 weeks	Early physical therapy usually successful in 2–3 months; orthopedic referral if persists
Skin		
Umbilical cord granuloma	Vascular, red/pink granulation tissue after cord separation	Apply silver nitrate one to three times protecting surrounding skin; excise if persists
Pustular melanosis	Erythematous maculopapulo-pustular rash of face and trunk, unclear etiology	Observation
Café-au-lait spots (flat, light brown macules; usually <2 cm)	Consider neurofibromatosis if more than four spots larger than 5 mm	No treatment if few in number
Hemangiomas (often raised, red, vascular nodules, deeper lesions appear blue; usually <4 cm; onset during first 3–4 weeks, increases over 6–12 months)	Multiple lesions suggest possible dissemination involving internal organs	Most involute and disappear by 5 years of age; observe without treatment unless involving vital structures (may give propranolol in these cases), ulceration, or infection; evaluate further if multiple
Mongolian spots (gray-blue plaques, up to several centimeters, often lumbosacral, may appear elsewhere)	Hyperpigmentation, seen in up to 70% of nonwhite infants	Benign; most fade over first year; document location since sometimes confused with abuse during infancy
Nevi (variably sized light to dark congenital; brown macules; some others appear later during infancy)	Congenital giant (>20 cm) may undergo malignant degeneration	No treatment needed, although some advise removal of congenital nevi at puberty; refer giant nevi for evaluation
Petechiae (normal only on head or upper body after vaginal births)	Infection or hematologic problem if abnormal	If abnormal, check CBC and look for signs of TORCH syndrome
Port-wine stains (permanent vascular macules)	Possible associated ocular or central nervous system (CNS) abnormalities	Cosmetic problem only, unless other abnormalities found
Subcutaneous fat necrosis (hard, purplish, defined areas on cheeks, back, buttocks, arms, or thighs, appearing during the first week)	Necrosis of fat from trauma or asphyxia	Spontaneous resolution over several weeks; rare complication of fluctuance or ulceration
Abdomen/gastrointestinal		
Mass	Genitourinary (GU) in 50% (either kidney or bladder), can be GI origin as well	Emergent ultrasound (US) of urinary tract
Single umbilical artery	2–4% have other congenital defects, especially cardiac and renal	Careful clinical exam for other defects, consider renal ultrasonography
Delayed passage of meconium (99% of healthy term neonates pass meconium within 24 h)	Small bowel obstruction with bilious vomiting (atresias, malrotations, meconium ileus) or large bowel obstruction (Hirschsprung's, anorectal atresias, meconium plug syndrome)	Anal inspection and rectal exam; if distended, abdominal X-ray and consider contrast enema, rectal biopsy; vomiting, bilious emesis, or distention requires rapid surgical evaluation

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Table 1 (continued)

Abnormality	Causes	Evaluation/treatment
Intestinal atresia (bilious vomiting with variable degrees of distention)	If duodenal, resorption of lumen occurred. If jejunoileal, mesenteric vascular injury	Replogle tube to low intermittent suction, lab, abdominal X-ray; contrast enema; surgery
Meconium ileus (distended at birth, X-ray with distended loops and bubbly picture of air/stool in right lower quadrant; absent air/fluid levels)	Abnormal meconium trapping resulting in small bowel obstruction; often associated with cystic fibrosis; may be associated with small for gestational age/intrauterine growth restriction	Abdominal X-ray; consider gastrografin enema (successful in two thirds), otherwise surgery; consider referral to a pediatric pulmonologist, check sweat chloride test or newborn screening result
Meconium plug syndrome (most common distal obstruction)	Inspissated colorectal meconium; diffuse gaseous distention of intestinal loops on X-ray; no air fluid levels	Abdominal X-ray; contrast enema is diagnostic and often therapeutic; search for other causes if symptoms continue
Genitourinary tract		
Ambiguous genitalia (if gonads are palpable, likely to be male)	Virilization of genetic female (esp. congenital 21-hydroxylase deficiency) or undermasculinized male	Obtain blood for chromosomal analysis, may consider buccal smear and 17α-hydroxy-progesterone; withhold diagnosis of sex until karyotype complete
Hypospadias (urethral opening proximal to tip of glans; may be associated chordee: abnormal penile curvature)	Isolated defect unless other GU anomalies present; 10–15% have first-degree relative with hypospadias	Avoid circumcision; repair 6–12 months of age by experienced surgeon; check for cryptorchidism and hernia; siblings at increased risk
Cryptorchidism (failure of testicular descent; 20% bilateral; long-term complications of infertility and cancer if left untreated)	May be normal: seen in 30% of preterm, 4% of term; if bilateral, consider ambiguous genitalia; if hypospadias and bilateral, consider urologic or endocrine problems	Observe for descent by 6 months; if not, treatment by 1 year of age; if bilateral, obtain karyotype; if also hypospadias, do full urologic and endocrine evaluation
Hydrocele (scrotal swelling that transilluminates but does not reduce during the exam)	Persistence of processus vaginalis distally without communication to the abdominal cavity	If no hernia, most spontaneously resolve in 3–12 months; prompt surgical referral if hernia or increasing size; persistence beyond 1 year makes hernia likely
Inguinal hernia (inguinal bulge that extends toward or into the scrotum; larger with crying or straining)	Processus vaginalis persists and communicates with abdominal cavity	If reducible, prompt referral for surgery to avoid incarceration; if irreducible, emergent referral
Testicular torsion	Idiopathic	Emergent evaluation with ultrasonography and surgery
Musculoskeletal		
Syndactyly (fusion of two or more digits)	Sporadic or autosomal dominant	Depending on site, surgery between 6 and 18 months of age
Polydactyly (more than five digits)	Sporadic or autosomal dominant	If no cartilage/bone, remove early, otherwise referral to plastic surgery for evaluation and removal
Metatarsus adductus (forefoot supinated and adducted; may be flexible or rigid; ankle range of motion must be normal)	Hereditary "tendency," but often due to uterine crowding; 10% association with hip dysplasia, requires careful exam	If flexible and overcorrects into abduction, no treatment; if corrects only to neutral, use corrective shoe for 4–6 weeks and reassess; if rigid, needs early casting
Talipes equinovarus (clubfoot; variably rigid foot, calf atrophy, hypoplasia of tibia, fibula, and foot bones)	Multifactorial with autosomal dominant component; 3% risk in sibs and 20–30% for offspring of affected parent	Anteroposterior (AP) and stress dorsiflexion lateral X-ray; early serial casting; if persists, surgery by 6–12 months (90% success rate)

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Table 1 (continued)

Abnormality	Causes	Evaluation/treatment
Nervous system		
Spina bifida occulta (spinal defect with cutaneous signs: patch of abnormal hair, dimple, lipoma, hemangioma)	Nonfusion of posterior arches of spine; may be tethering of cord or sinus to spinal space with risk of infection; clinical exam for other defects	Examine for neurologic deficits; US to document defect if cutaneous signs; nonemergent referral to neurosurgeon if dermal sinus or tethering suspected; prompt referral if deficits present

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Guidelines for Early Hospital Discharge of the Newborn

Hospital stays should be long enough to identify early problems and ensure the family is ready to care for the infant at home. Most states recommend and require insurance coverage for a hospital stay up to 48 h for a vaginal delivery and up to 96 h for a cesarean delivery.

Many factors should be included when evaluating a newborn for discharge to home from a maternity facility. These include the following: no significant abnormalities noted on exam, vital signs normal for 12 h prior to discharge, urination and passage of at least one stool, two successful consecutive feeds, no clinically significant hyperbilirubinemia, and adequate follow-up arrangements have been made, either within 24–48 h from hospital discharge or by the 3rd to 5th day of life depending on assessment of risk or need. In addition, the newborn should have been adequately monitored for sepsis; maternal screening labs were within normal limits or addressed; hepatitis B vaccine has been administered (along with hepatitis B immune globulin if the mother is hepatitis B surface antigen positive); newborn metabolic, hearing, and congenital heart screens have been completed; the mother's ability to care for infant was assessed; family and home situation is deemed safe for the infant; follow-up for the infant has been established; and, finally, both the pediatrician and obstetrician agree with the discharge plan [24].

Well-Child Visits

Well-child visits are an important time for the provider to establish relationships with both the family and patient. It is a time for anticipatory guidance, answering parental concerns and delivering patient care, including screenings and immunizations. Each visit also includes an age-appropriate physical exam, growth parameter assessment using the WHO growth standards for infants, nutritional assessment, standardized screening, developmental milestone assessment, and anticipatory guidance. These visits begin 2–3 days after hospital discharge and continue at 1–2 weeks of age and then at 1, 2, 4, 6, 9, and 12 months of age. The full schedule can be found online from the AAP [25], and further information is present in ▶ Chap. 6, "Clinical Prevention."

Nutrition and Feeding

Breastfeeding

The AAP recommends exclusive breastfeeding for about the first 6 months of life as well as continued breastfeeding in addition to complementary solid foods for a minimum of 1 year, or as long thereafter as mother and infant mutually desire to continue breastfeeding [11]. The American Academy of Family Physicians indicates that health outcomes for mothers and babies are best when breastfeeding continues for at least 2 years [26]. The role of the physician is to encourage

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mother and family to pursue breastfeeding the infant if no medical contraindications exist and to provide information on benefits and risks compared to formula feeding.

The benefits of breastfeeding include immunologic protection for the infant, development of optimal intestinal microbiota, and optimization of attachment between mother and infant. Breastfeeding is associated with lower rates of acute otitis media, lower respiratory tract infections, gastrointestinal infections, NEC, sudden infant death syndrome (SIDS), asthma, and obesity in children [11]. Maternal benefits of breastfeeding include reduced risks of type 2 diabetes mellitus and hypertension, as well as breast, ovarian, and endometrial cancers [27].

The primary care physician's role in encouraging exclusive breastfeeding is extremely important and ideally should begin prenatally. Physicians should encourage implementation of optimal maternity care practices to support breastfeeding mothers and newborns in the delivery facility and in office practices. All staff should be trained about breastfeeding so they can provide evidence-based guidance and support. Likelihood of breastfeeding success improves with ensuring immediate skin-to-skin contact and initiation of feeding within the first hour of life. Providers and other health-care staff should observe mothers when breastfeeding and help them modify techniques if difficulties occur. Trained lactation specialists may be helpful in these situations. Newborns should practice rooming-in throughout the hospital stay. Formula should be provided only if medically indicated. Infant formula samples should not be provided at hospital discharge or in the office. Educational materials should not promote commercial infant formula [11].

There are very few absolute contraindications to breastfeeding. These include infants with galactosemia and mothers with active herpes lesions on the breasts, who are HIV or HTLV-1 or HTLV-2 positive, and/or who are using illicit substances. Mothers with untreated tuberculosis should avoid direct contact with the infant but may express milk for feeding until the mother has initiated treatment and has negative sputum cultures [11]. With emerging pathogens, the AAP Committee on Infectious Diseases and the CDC issue guidance regarding the risks and benefits of breastfeeding. All mothers should be up to date on immunizations to confer passive immunity to the infant.

Vitamin D Supplementation

Vitamin D is important for newborns and infants, and a deficiency is associated with rickets and other metabolic problems. Newborns and infants should receive 400 IU of vitamin D each day [28]. Either breastfed infants should be supplemented with 400 IU beginning at hospital discharge [28], or alternatively, maternal intake of 6400 IU of vitamin D daily will raise levels of vitamin D in breast milk to a sufficient level for the infant [29].

Infant Formula

After informing mothers about the benefits of breastfeeding, the families' infant feeding decision should be respected and supported. Providers should avoid appearing judgmental if the mother chooses to feed infant formula. A standard commercially available bovine-based infant formula is most commonly used and tolerated well by most infants. Alternative formulas can be considered in special circumstances. When bottle feeding is chosen, counsel mothers and monitor for the common tendency to overfeed the infant.

Advancing the Infant Diet

For the first 12 months of life, infants should continue to receive human milk or infant formula. Introducing cow's milk earlier increases the risk of iron deficiency anemia and occult gastrointestinal bleeding [30]. At 12 months, infants may continue breastfeeding or replace infant formula with either whole or 2% milk, switching to 1% or skim milk by age 2. Toddler formulas are not recommended.

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Complementary solids may be added to breast milk or formula when the infant (1) exhibits good head control when sitting, (2) is able to sit up with minimal assistance, (3) shows interest in food such as opening the mouth in response to seeing the spoon coming close, and (4) can indicate fullness or refusal by turning the head. Typically, these developmental milestones appear between 4 and 6 months of age. In general, introduction of solids should begin at about 6 months of age from nutritional and developmental standpoints. Families gradually can introduce the older infant to pureed or finely minced foods that the family enjoys. Excessive salt, sugar, and less healthy fats should be avoided.

For infants at high risk of peanut allergy, peanut protein should be introduced before 6 months of age, as it has been shown to reduce the incidence of peanut allergy [31]. Fruit juice should be avoided in infants under the age of 12 months. Between 1 and 3 years of age, the recommendation is no more than 4 oz of juice and only from a cup, not a bottle [32]. Water should be encouraged as the beverage of choice.

Infant Colic

Approximately 10–26% of infants will experience colic. It is described as crying without an etiology for >3 h/day, >3 weeks in duration, beginning before the third week of life. Colic peaks at 6 weeks and tends to resolve by about 3 months of age. The diagnosis is made by taking a good history and performing a complete physical examination. Differentials to consider include constipation, gastroesophageal reflux disease, feeding disorders, acute abdominal pain, occult fracture, and drug withdrawal syndromes [33].

There is no definitive treatment for colic. First-line therapy is parental reassurance and behavioral interventions. Such interventions include sucking, effective swaddling, gentle rocking, and decreased stimulation of the infant. Simethicone is not effective in the treatment of colic. Soy, iron-free, or lactose-free formulas have not been shown to improve colic [33].

Failure to Thrive

Failure to thrive (FTT) occurs when a child receives inadequate nutrition for optimal growth and development, manifested by weight less than third or fifth percentile for age on more than one consecutive occasion, weight dropping down two major percentile lines on the growth chart, weight <80% of the ideal weight for age, and/or the child less than the third or fifth percentile on weight-for-length curves. Infants with intrauterine growth restriction are known to be at risk for subsequent failure to thrive [34]. Three major categories that cause FTT are inadequate intake, malabsorption or excessive gastrointestinal losses, or increased metabolic demand.

Examples of inadequate intake include not enough food being offered, or the child not taking enough food secondary to oral motor dysfunction, developmental delay, or another feeding disorder. Emesis secondary to gastroesophageal reflux or increased intracranial pressure can also result in FTT. Common causes of malabsorption associated with FTT include cystic fibrosis, celiac disease, or food protein intolerance. These may manifest as frequent, loose stools or frank diarrhea. Examples of increased metabolic demand include insulin resistance, congenital infections, certain syndromes (Turner, Down), or chronic diseases (cardiac, renal, endocrine).

Initial workup includes an accurate history of nutritional intake using a 3-day food diary, ideally in consultation with a nutritionist. Laboratory evaluation includes a CBC, complete chemistry panel, celiac screening, stool examination for fats and reducing substances, and a sweat chloride test. In cases of severe malnutrition, the child may need to be admitted to the hospital for evaluation and treatment [34]. All children should be screened for eligibility for nutritional assistance from the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) up to 5 years of age. Pregnant and breastfeeding women also are eligible for WIC benefits.

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Fever

Self-limited viral infections are the most common cause of fevers in infant. The younger the infant, the greater concern for the potential of a serious infection with a fever. Infants <3 months of age with no obvious source of fever have an 8.5% risk of having a serious bacterial infection (SBI). Serious bacterial infections include conditions such as sepsis, pneumonia, pyelonephritis, and meningitis that can be life-threatening. The provider must have a reliable system to identify those at risk for a SBI [35].

Neonates (0–28 Days)

A neonate with a rectal temperature of 38 °C or 100.4 °F should be considered a relative emergency and prompt a full evaluation for SBI. Laboratory testing should include CBC with differential, cerebrospinal fluid (CSF), blood, and urine cultures. Admission for empiric intravenous antibiotics is ensured until cultures are negative, or for a full antibiotic course if indicated from laboratory results or patient symptoms.

Ill-Appearing Infants (29–90 Days)

12.8% of ill-appearing febrile young infants may have an SBI. Therefore, these infants should also have CSF, blood, and urine cultures drawn and be admitted for empiric intravenous antibiotics.

Well-Appearing Infants (29–60 Days)

Infants with fever at this age still require laboratory screening for SBI. Generally, evaluation should include a CBC, as well as blood and urine cultures. If the infant is well-appearing, there is low suspicion of an SBI on initial exam, and good outpatient follow-up is available, then it is not necessary to admit these patients.

Infants 61–90 Days Old

If the infant is well-appearing, then the basics of CBC, blood, and urine cultures are obtained with outpatient follow-up. If the infant is ill-appearing and suspicion for SBI is high, then a full evaluation for sepsis and empiric antibiotics with admission to the hospital is warranted.

Infants 3–36 Months Old

For infants with fevers less than 39 °C in this age range, a SBI is less likely. If there are multiple days of high fevers, worsening clinical picture, and no source of infection identified during a careful physical examination, then a CBC is warranted. If it is normal, the infant can be observed closely, but if abnormal, consideration should be given to further workup with blood and urine cultures. Most children with fevers at this age have a viral infection. Otitis media may be seen on examination, especially if symptoms of a preceding upper respiratory tract infection were present.

Sudden Infant Death Syndrome

SIDS, also described as sudden unexpected infant death, is the second leading cause of infant mortality between 1 month and 1 year of age in the United States. SIDS is defined as a sudden, unexpected death before 12 months of age that occurs in a previously healthy infant, in which case the cause of death remains unknown despite a thorough case investigation, including a complete autopsy, death scene investigation, and analysis of clinical history. Each year, 2300 infants die from SIDS in the United States, and the rate peaks between 3 and 5 months of age. Since the "Back to Sleep" campaign was initiated in 1994, the incidence of SIDS has declined between 30% and 50%.

Risk factors include maternal, infant, and environmental factors. Maternal factors include young age, maternal smoking during and after pregnancy, and limited or no prenatal care.

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Infant risk factors include preterm birth and/or low birth weight and male gender. Environmental factors include prone sleeping, sleeping on a soft surface and/or excessive bedding and pillows, co-sleeping, crib bumpers, entrapment when sleeping on couches or chairs, and overheating.

Sleep positioning has been found to be the strongest modifiable risk factor for SIDS, with supine sleeping recommended. Other factors that decrease risk of SIDS include breastfeeding and the use of pacifiers. Apnea monitors are not recommended as they have not been shown to reduce the risk of SIDS. It is important to educate parents in a nonjudgmental way and to reaffirm safe sleep recommendations at every visit during the infant's first year of life. Ideally, the infant should sleep on their own firm sleep surface in the parent room [36, 37].

Brief Resolved Unexplained Event

A brief resolved unexplained event (BRUE) is defined as an event occurring in infants younger than 12 months of age. These episodes previously had been referred to as "Apparent Life Threatening Events" (ALTE). The episodes are described by the observer as brief, resolved, and with a reassuring history, physical exam, and vital signs at the time of clinical evaluation by trained medical providers. "Brief" indicates that the episode lasts less than 1 min, but more often is <20–30 s, and "resolved" refers to the patient being back to baseline after the event.

There are four characteristics that can be described by an observer for a BRUE, and at least one must be described in order to call the event a BRUE: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone; and/or (4) altered level of responsiveness. If a patient is found to have an alternate diagnosis, such as reflux or seizures, then a BRUE is not diagnosed. Evaluation and management is focused on the presumed diagnosis.

BRUE cases that are classified as being at lower risk for serious outcomes include infants greater than 60 days old, those born at greater than 32 weeks of gestational age, and those born with no concerning findings during history and exam, such as evidence of abuse or trauma. These infants typically do not need admission. Higher-risk BRUE is defined as any patient that falls outside of the lower-risk definition. Admission should be determined by the provider on an individual basis [37].

Other Common Problems of the Infant

Table 2 provides a brief synopsis of additional common problems of infancy encountered by the primary care physician.

Family and Community Issues

Perinatal Depression

Perinatal depression, also known as perinatal mood disorder, is defined as an episode of major depressed mood and neurovegetative symptoms such as alterations in sleep and appetite during pregnancy or after delivery. It can affect up to 20% of new mothers.

There are many long-lasting and sometimes permanent consequences from untreated depression, such as deterioration of social networks and partner relationships, poor family functioning, increased risk of child abuse and neglect, delayed infant development, and challenges with breastfeeding. Children can develop physical, emotional, cognitive, and social problems.

One assessment used to screen for perinatal depression is the Edinburgh Postnatal Depression Scale. Mothers are comfortable being screened for depression, but a large percentage do not openly speak to health-care professionals about their symptoms. Screening for postpartum depression is recommended during well-child visits at 1, 2, 4, and 6 months, with referral as appropriate for those with positive screens [38].

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Table 2 Approaches to common problems of the infant. Recommend consulting pediatric formulary (e.g., Harriet Lane Handbook) for current drug doses

HEENT (head, ears, eyes, nose, and throat)
Thrush (pearly white pseudomembranes on the oral mucosa). Causes: transmission from vaginal mucosa during delivery; contaminated fomites (nipples, both breast and bottle; toys; teething rings). Rx: clean fomites (boil bottle nipples, toys); oral nystatin, 200,000–500,000 U q4–6 h until clear for 48 h
Nasolacrimal duct obstruction (see Table 1). Symptoms usually delayed until days to weeks after birth. Rx: nasolacrimal massage three to four times per day with clean hands and cleansing of eyelids with warm water; topical antibiotics (sulfacetamide or gentamicin drops) for secondary conjunctivitis
Strabismus (misalignment of eyes). Screen with corneal light reflex and cover test. Rx: ophthalmology referral for persistent deviation greater than several weeks or any deviation >4 months of age
Hearing loss. Universal screening recommended after delivery by American Academy of Pediatrics Risk factors include family history; congenital infection; craniofacial abnormalities; birth weight < 1500 g; hyperbilirubinemia requiring exchange transfusion; severe depression at birth; bacterial meningitis. Screening: otoacoustic emissions testing or auditory brainstem response. Treatment by 6 months can greatly improve future language development. Infants not passing should have an audiologic evaluation by 3 months (or by 6 weeks if CMV is the potential etiology)
Teething (painful gums secondary to eruption of teeth with irritability, drooling). Fever is not caused by teething. Rx: chewing on soft cloth, teething ring; systemic analgesia
Skin problems
Circumcision. Elective procedure performed only on healthy, stable newborns using a penile block. Contraindicated if any genital abnormalities. Advantages: decreased incidence of phimosis, urinary tract infection, and penile cancer (later in life). Risks: hemorrhage; sepsis; amputation; urethral injury; removal of excessive foreskin with painful scarring
Diaper dermatitis (erythematous, scaly eruptions that may advance to papulovesicular lesions or erosions; may be patchy or confluent; genitocrural folds often spared). Due to reaction to overhydration of skin, friction, and/or prolonged contact with urine, feces, chemicals such as in diapers and soaps. Rx: frequent changing of diapers; exposure to air; bland, protective topical ointment (petrolatum, zinc oxide) after each diaper change; advanced cases may require 1% hydrocortisone ointment
Candidal superinfection (pronounced erythema with sharp margins, satellite lesions, involvement of genitocrural folds). Rx: topical antifungal; treat associated oral candidiasis
Milia (superficial 1–2 mm inclusion cysts). Common on face and gingiva. Requires no Rx
Miliaria (clear or erythematous papulovesicles in response to heat or overdressing; especially in flexural areas). Resolves with cooling
Seborrheic dermatitis (most commonly greasy yellow scaling of scalp or dry white scaling of inguinal regions; may be more extensive). Rx: generally clears spontaneously; may require 1% hydrocortisone cream; mild antiseborrheic shampoos for scalp lesions; mineral oil with gentle brushing after 10 min for thick scalp crusts
Atopic dermatitis (intensely pruritic, dry, scaly, erythematous patches). Acute lesions may weep. Typically involves face, neck, hands, abdomen, and extensor surfaces of extremities. Genetic propensity with frequent subsequent development of allergic rhinitis and asthma. Consider evaluation for food and other allergens. Rx: mainstay is avoidance of irritants (temperature and humidity extremes, foods, chemicals) and drying of the skin (frequent bathing, soaps) with frequent application of lubricants (apply to damp skin after bathing); severe disease usually requires topical steroids; acute lesions may require 1:20 Burrow's solution and antihistamines (diphenhydramine, hydroxyzine)
Heart murmur
Innocent or functional (typically diminished with decreased cardiac output)
Newborn murmur. Onset within first few days of life that resolves by 2–3 weeks of age. Typically soft, short, vibratory, grade I–II/V early systolic murmur located at lower left sternal border that subsides with mild abdominal pressure
Still's murmur. Most common murmur of early childhood. May start in infancy. Typically loudest midway between apex and left sternal border. Musical or vibratory, grade I–III early systolic murmur
Pulmonary outflow ejection murmur. May be heard throughout childhood. Typically soft, short, systolic ejection murmur, grade I–II, and localized to upper left sternal border
Hemic murmur. Heard with increased cardiac output (fever, anemia, stress). Typically grade I–II high-pitched systolic ejection murmur heard best in aortic/pulmonic areas
Pathologic or organic murmurs. Any diastolic murmur. Consider when a systolic murmur has one or more of the following: grade III or louder, persistent through much of systole, presence of a thrill, single second heart sound (most important finding), abnormal quality of second heart sounds (loud, "click"), or a gallop. Other ominous signs:

(continued)

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Table 2 (continued)

congestive heart failure, cyanosis, tachycardia. Evaluation: chest X-ray (CXR), electrocardiogram (ECG), consider arterial blood gas, and if persistent or any distress then cardiology consult
Gastrointestinal
Constipation (intestinal dysfunction in which the bowels are difficult or painful to evacuate). Associated failure to thrive, vomiting, moderate to tense abdominal distention, or blood without anal fissures requires ruling out organic disease (Hirschsprung's, celiac disease, hypothyroidism, structural defects, lead toxicity). Common causes are anal fissures, undernutrition, dehydration, excessive milk intake, and lack of bulk. Less common with breastfeeding. Rarely caused by iron-fortified cereals. Rx: in early infancy increase amount of fluid or add sugars (Maltsupex); later add juices (prune, apple) and other fruits, cereals, and vegetables; may add further artificial fiber (psyllium); severe disease may require use of polyethylene glycol electrolyte solutions (dose varies according to situation) and brief use of milk of magnesia (1–2 tsp.), docusate sodium, and glycerin suppositories and when persistent requires ruling out of organic disease
Gastroesophageal reflux (GERD). Vomiting noted in 95% of infants within the first 6 weeks, resolving in 60% by age 2. Important to distinguish "spitting up" from true GERD. Spitting up is not associated with significant weight loss, breast milk or formula intolerance, or other warning signs. GERD may be associated with growth delay, esophagitis, hemoccult positive stool, chronic cough, and wheezing. Consider cow's milk allergy. Dx: mild cases confirmed by history and therapeutic trial. If more severe, esophageal pH probe and barium fluoroscopic esophagography. Endoscopy if esophagitis is suspected. Rx: elevate head of bed for older infants. Consider thickened feedings with cereal. Refer with persistent severe symptoms
Pyloric stenosis (nonbilious vomiting immediately after feeding becoming progressively more projectile). 4:1 male/female preponderance. Onset 1 week to 5 months after birth (typically 3 weeks). More common in males. May be intermittent. Dx: palpation of pyloric mass (typically 2 cm in length, olive shaped) that may be easier to palpate after vomiting; ultrasound is preferred method to confirm difficult cases (90% sensitivity). Rx: surgery after rehydration
Anemia
Improved nutrition has reduced incidence, but infants remain at significant risk. Additional risk factors: low socioeconomic status, significant maternal anemia, consumption of cow's milk prior to age 6 months, use of human milk substitute that is not iron fortified, low birth weight, prematurity. Effects: fatigue, apathy, impairment of growth, and decreased resistance to infection. Causes: iron deficiency most common (usually sufficient birth stores to prevent occurrence prior to age 4 months), sickle cell disease, thalassemia, lead toxicity. Screening: hemoglobin (Hgb) or hematocrit (Hct) at age 12 months (some recommend only for infants with risk factors). Rx: if microcytic give trial of iron (elemental iron, Feosol, 3–6 mg/kg/day); if not microcytic or unresponsive to iron, consider other causes (family history, environment)
Sleep disturbances
Seventy percent of infants can sleep 5 or more hours of the night by age 3 months. Most 6-month-olds no longer require nighttime feeding. Screening: a sudden change in sleeping pattern should prompt a search for new stresses, physical (infection, esophageal reflux, etc.) or emotional (new surroundings or household members, etc.). Rx: establish realistic parental expectations (consider the natural sleeping patterns of the infant); allow the infant awakening at night to learn how to fall asleep by himself (keep bedtime rituals simple and put the infant in his bed awake; do not respond to infant's first cry; keep interactions during the night short and simple; provide a security object for older infants); slowly change undesirable sleeping patterns (move bedtime hour up and awaken infant earlier in the morning; decrease daytime napping)

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Child Care

Many young children spend time in child care. It is recommended that all children and providers be up to date on immunizations to reduce the risk of transmissible infections [25]. On average, children get between 8 and 12 viral infections in the first year of child care. That number typically decreases in the second year due to exposure and subsequent immunity [39]. Parents should interview caregivers to make sure that the values and child-rearing philosophies are consistent with their own and that their child will be in a safe environment.

Family Violence

Family violence is defined as acts of violence that occur among family members such as partners,

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siblings, caregivers, and children. Child maltreatment is more common when the mother's partner is not the child's biological father.

Children who are exposed to violence have a range of physical and behavioral health problems. They have a higher likelihood of school and learning difficulties, drug and alcohol use, engaging in prostitution, committing sexual assault, running away from home, and attempting suicide. Children exposed to violence also are more likely to engage in violent behavior themselves. Family violence is only one type of adverse childhood experience with long-lasting consequences.

Screening questions include (1) has your partner ever injured or threatened to injure your children, (2) are you an equal partner when it comes to making important decisions that affect your family, and (3) what happens when you and your partner have a disagreement [40].

Substance-Exposed Infants

Children of substance-using parents are at increased risk for suffering abuse and neglect. Up to one in five children grows up in a home in which someone abuses drugs or alcohol. Almost 25% of these children do not receive routine health maintenance in the first 2 years of life.

Approximately 32,000 infants born annually in the United States are diagnosed with neonatal abstinence syndrome. This number represents a fivefold increase in recent years and is associated with a significant increase in the cost of health care [41]. Symptoms of prenatal opioid use may manifest in infants as sweating, irritability, increased muscle tone, feeding problems, and seizures as a result of opioid withdrawal. Fetal alcohol exposure can cause prematurity and low birth weight as well as affect growth, cognition, behavior, language, and achievement. Management of substance-exposed neonates should include consultation with neonatal specialists and team-based care and support, as well as referral for appropriate developmental follow-up. The primary care provider may assist families by providing access to resources and should report families to the appropriate authorities if child maltreatment is suspected [42].

Adolescent Parents

Many adolescent mothers have medical and psychosocial risks. Medical complications include poor maternal weight gain, anemia, and pregnancy-induced hypertension. Psychosocial risks include violence during pregnancy, poorer educational outcomes, and future economic difficulties. Factors that improve outcomes for adolescent mothers include actively participating in a program for teenage mothers, remaining in school, and avoiding social isolation [43].

Medical complications of infants born to adolescent mothers include higher incidence of perinatal mortality, low birth weight, preterm birth, developmental disabilities, and poorer developmental outcomes. The role of the primary care physician should be to maintain continuity with the adolescent mothers and care for their children, if possible. They should encourage use of community resources to teach young parents the basic caregiving skills they need and ensure they provide a safe environment for a child. Discussing contraception and prevention of sexually transmitted infections with adolescent parents is also important [43].

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Infectious Diseases in Children

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Introduction

Infectious diseases are one of the most frequent reasons for pediatric consultations. Although mortality and morbidity from infectious diseases have dramatically declined in recent years, infections among children remain important.

Like many other diseases in children, the complications of the disease such as dehydration might be the primary focus of management rather than treating the causative agent, as many infectious diseases in children are self-limiting.

This chapter will discuss some of the more prevalent infectious diseases in children in addition to some that are less common but should not be missed.

Common Cold

General Principles

Definition/Background

The common cold is an acute, self-limiting viral infection of the upper respiratory tract characterized by variable degrees of sneezing, nasal congestion and rhinorrhea, sore throat, cough, low grade fever, headache, and malaise [1].

Epidemiology

The common cold is the most common infectious disease among children. A healthy child may develop upper respiratory tract infections (URTI) six to eight times per year [2]. Infants and children may experience more prolonged symptoms than adults. Common colds are most commonly caused by rhinovirus, which accounts for about 60% of infections. Other causes include parainfluenza, respiratory syncytial virus, coronavirus, adenovirus, echovirus, coxsackievirus, and parainfluenza virus [3].

Approach to the Patient Diagnosis, History, and Physical Examination

The diagnosis of the common cold is based on symptoms. Symptoms usually peak on day 2–3 of the illness and gradually improve over the next 10–14 days. An associated cough may linger in a minority of children but typically resolves over 3–4 weeks [1, 4]. Fever is uncommon, although temperatures of up to 39 °C may occur in younger children. A red nose with a profuse nasal discharge may be present. The discharge can be clear and watery or mucopurulent (yellow or green). Purulent secretions are more common after the first few days of illness.

Differential Diagnosis

The common cold should be distinguished from allergic rhinitis, isolated pharyngitis, acute bronchitis, influenza, bacterial sinusitis, or pertussis [5].

Treatment

Current guidelines on the treatment and management of respiratory tract infections (RTIs) in children emphasize supportive management. This includes hydration, nasal suction, saline nasal drops, spray, or irrigation. A cool mist humidifier may be helpful. Parents may give acetaminophen to children older than 3 months or ibuprofen to children older than 6 months to treat the discomfort associated with any fever. Over-the counter (OTC) medications such as cough medications or antihistamines are not recommended for young children. As most RTIs are caused by viruses, antibiotics should only be prescribed if an RTI is suspected to be of bacterial origin.

Zinc, vitamin C, and herbal products such as echinacea are advertised to treat or prevent the common cold. There is some evidence that prophylactic use of vitamin C may decrease the duration of the common cold in children. However, with the exception of vitamin C, none of these treatments have been proven to be effective in clinical trials and thus their use is not recommended [6].

Complications of the common cold include acute otitis media, acute bacterial sinusitis, asthma exacerbation, and lower respiratory tract disease. Re-evaluation may be warranted if the symptoms

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worsen (e.g., difficulty breathing or swallowing, high fever) or exceed the expected duration.

Immunizations and Chemoprophylaxis

The Centers for Disease Control and Prevention (CDC) recommends a yearly flu vaccine as the first and most important step in protecting against influenza and its potentially serious complications. All children 6 months and older should receive the influenza vaccine every year before flu activity begins in their community [7].

Prevention

The best methods for preventing transmission of the common cold are frequent hand washing and avoiding touching one's mouth, nose, and eyes. Most children with colds need not be excluded from out-of-home childcare or school because transmission is likely to have occurred before the child became symptomatic [1].

Family and Community Issues

The common cold accounts for approximately 22 million missed days of school and 20 million absences from work, including time away from work to care for ill children.

Common Pediatric Viral Exanthems

General Principles

Definition

An exanthem is a term used to describe skin lesions associated with other systemic manifestations like fever. Exanthems can be caused by infections or allergic reactions to medications or to other agents. Viral infections account for the majority of cases of exanthems in children.

Classification

Pediatric viral exanthems can be classified based on the presentation of the skin lesions, into maculopapular and vesicular rashes. Viral exanthems that manifest with a maculopapular rash include measles, rubella, roseola infantum, and erythema infectiosum. Conversely, varicella and hand-foot-and-mouth disease (HFMD) present with papulovesicular rash.

Diagnosis

History and Physical Examination

Differentiation should be based on the morphologic appearance of the lesions, their distribution and order of appearance, their relation to fever, and the presence of other associated physical findings that can be characteristic and sometimes pathognomonic for a specific viral illness. Diagnosis of pediatric viral exanthems is largely based on the clinical presentation and a good history. Laboratory evaluation is usually not necessary.

Measles

Epidemiology

Measles is a highly contagious disease caused by a paramyxovirus which carries high risk of serious complications and fatalities. Following the introduction of the measles vaccine in 1963 the disease has dramatically declined. However, provisional data from the World Health Organization (WHO) indicates that during the first 6 months of 2019 there have been more measles cases reported worldwide than in any year since 2006 [8].

Patient Approach

Clinical Presentation

Measles virus can be acquired via respiratory droplets from infected individuals. After an incubation period of 1–3 weeks, patients have a two-to-four-day prodromal phase characterized by fever, malaise, cough, coryza, conjunctivitis, and Koplik spots. These spots are pathognomonic for measles infection. They appear as

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small, grayish white papules in the buccal mucosa opposite to the molar teeth and have been described as "grains of salt on a red background." They can last for 12–72 h and start to disappear with the onset of a skin rash. The maculopapular rash first appears in the preauricular area then spreads centrifugally to the rest of the body. The fever usually persists for 3 days after the onset of rash. After 6–7 days the rash starts to disappear in the same order of its appearance. Infection usually results in lifelong immunity, although in rare cases reinfection may occur and present with modified measles having milder clinical manifestations.

Complications

Measles infection can be complicated by a decline in T-cell related immune response leading to an increased risk of infections during and shortly after measles infection. Common complications include gastroenteritis, otitis media, pneumonia, and other respiratory complications. Pneumonia is the most common life-threatening complication. Measles infection can also affect the central nervous system, leading to acute encephalitis, acute disseminated encephalomyelitis (ADEM), and subacute sclerosing panencephalitis (SSPE). Acute encephalitis usually occurs within a few days of the appearance of a rash and is directly due to viral infection. Conversely, ADEM is thought to be a post-infectious autoimmune response. It may also be triggered by other infectious agents, but it carries a higher mortality rate when it follows a measles infection.

SSPE manifests 7–10 years after measles infection and is characterized by progressive neurodegenerative changes. It is thought to be caused by persistent measles virus infection within the central nervous system. Measles-related complications may occur in up to 30% of cases in immunocompetent, and more frequently in immunocompromised patients, pregnant women, individuals with vitamin A deficiency, or in individuals younger than 5 years or older than 20 years [9].

Treatment

In addition to symptomatic treatment, Vitamin A administration once daily for 2 days reduces mortality and morbidity from measles. This is because vitamin A deficiency contributes to a delayed recovery and the high rate of postmeasles complications. In addition, acute vitamin A deficiency and xerophthalmia may be precipitated by measles infection [9]. Ribavirin may be considered for patients with measles-related pneumonia or patients with severe immunosuppression.

Prevention

A two-dose live attenuated measles vaccine is recommended as part of the MMR vaccine given after the child's first birthday. In addition, isolation of infected persons immediately upon making the diagnosis, and until 4 days after the onset of rash can help reduce viral transmission.

Rubella

Rubella is caused by infection by an RNA virus of the Togaviridae family. The infection is also known as "the three-day measles" or "German measles."

Epidemiology

After introduction of the rubella vaccine, there has been a significant drop in its incidence and complications. Sporadic outbreaks have been reported when vaccination rates lag.

Patient Approach

Clinical Presentation

The virus is transmitted via respiratory droplets. After an incubation period of 2–3 weeks, patients start to have mild prodromal symptoms for 1–5 days, such as a sore throat, low-grade fever, myalgias, and symmetrical posterior cervical

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lymphadenopathy, mainly in the postauricular and occipital regions. Then, a maculopapular skin rash starts to appear on the face and rapidly spreads in a craniocaudal manner. This rash typically lasts 3 days (thus the name "three-day measles"). However, nearly 50% of individuals are asymptomatic during infection. Arthritis or arthralgias occur in up to 70% of adolescents, particularly females.

Complications

Complications following rubella infection are infrequent. However, maternal infection during pregnancy can lead to intrauterine fetal death, preterm delivery or congenital rubella syndrome (CRS). The risk of CRS increases if maternal infection occurs early in pregnancy and is less likely if it occurs during the second half of the pregnancy. Infants with CRS can have heart defects, eye defects like congenital cataracts, neurodevelopmental disorders, and bilateral sensorineural hearing impairment.

Encephalitis can rarely follow rubella infection but is more likely to affect adults than young children. Coagulopathy leading to hemorrhagic complications tends to affect infected children more than adults [10].

Treatment and Prevention

Treatment is largely supportive as the disease usually has a mild course, especially among children. Rubella infection can be prevented by administering a live-attenuated rubella vaccine as part of the MMR vaccine given as two doses. Infected individuals are considered infectious from 7 days before the appearance of a rash to 7 days following its disappearance. Therefore, patients should be isolated for more than a week following the onset of a skin rash.

Varicella (Chickenpox)

Varicella is caused by a double stranded-DNA neurotropic virus from the Herpesviridae family. Primary infection can be followed by the dormant presence of the virus in the dorsal root ganglia of the spine which can be reactivated later in life with waning of cell-mediated immunity and manifest as a zoster infection (shingles) with its potentially incapacitating postherpetic neuralgia.

Epidemiology

Varicella occurs worldwide and, in the absence of a vaccination program, affects nearly every person by mid-adulthood. In areas with an implemented varicella vaccine programs, there have been drops in both incidence and complications. Chickenpox is considered highly contagious, with a secondary household attack rates of >90% in susceptible individuals.

Patient Approach

Clinical Presentation

The virus is acquired either via respiratory droplets or by direct contact with vesicular fluids of an affected individual. After an incubation period of 10–21 days, patients start to manifest mild prodromal symptoms like low-grade fever, malaise, and a sore throat, followed by the appearance of pruritic skin lesions within 24 h. Lesions first appear on the trunk or scalp and then spread centrifugally to the extremities. Mucous membranes in the mouth and conjunctivae can be also involved.

Lesions start as a macule that evolves into a papule and then into a vesicle filled with clear fluid, which eventually crusts. New crops of lesions continue to appear in the next few days. Thus, in the same area you can see the coexistence of papules, vesicles, and crusts at the same time, a finding characteristic of varicella. New vesicle formation generally stops within 4 days, and most lesions have fully crusted by day 6 in normal hosts [11]. After the disappearance of the crusts (usually 1–2 weeks later), they are replaced by hypopigmented macules which persist for some time.

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Complications

Varicella infection in immunocompetent children is considered to be a mild and self-limiting disease with a rare occurrence of serious complications. However, infants, adults, adolescents, and immunocompromised individuals are more prone to complications. The most common complication of varicella is bacterial superinfection of the lesions with invasive group A streptococcal or staphylococcal infection in the skin and subcutaneous tissue.

Pneumonia can also be a complication of varicella in adults and immunocompromised individuals. Encephalitis, aseptic meningitis, and transverse myelitis are the main neurologic complications of varicella. In addition, Reye syndrome was a complication observed among children who had been given a salicylate as an antipyretic during the infection. However, after cessation of the use of salicylates in children, it is now rarely seen.

If maternal infection occurs during pregnancy, transplacental transmission of the infection can ensue, leading to congenital varicella syndrome. This can result in low birth weight and multiple congenital abnormalities such as skin scarring, limb hypoplasia, eye abnormalities such as optic nerve atrophy and cataracts, microcephaly and mental retardation.

Treatment

In immunocompetent children, treatment is largely supportive as the infection tends to be self-limited. Acetaminophen is recommended to control fever and calamine lotion or other soothing lotions can be given to control pruritus. However, in adolescents, adults, immunocompromised patients, and children with chronic skin or lung diseases, acyclovir is indicated for 5 days starting within 24 h of rash onset to decrease the severity of symptoms and the disease duration.

Prevention

A live-attenuated vaccine for VZV has been available since 1995. It is administered as two doses at 12–15 months and at 5 years as part of the measles, mumps, rubella, and varicella (MMRV) vaccine or as a separate vaccine. Unvaccinated adolescents and adults who have no history of primary infection are advised to receive two doses of the vaccine separated by at least 28 days.

Patients are typically infectious from 48 h before the appearance of a skin rash until crusting of all the skin lesions, which usually takes place 1 week after the onset of the rash. Therefore, patients should be isolated for at least 1 week following appearance of the exanthem.

Roseola Infantum (Exanthema Subitum or Sixth Disease)

Epidemiology

This is a mild self-limiting disease caused by Human Herpes Virus 6 B (HHV6B) and less frequently by HHV6A and HHV7 viruses. It usually affects infants between 6 and 12 months of age, almost 90% of the cases are children under the age of 2. The virus is usually transmitted to the infant from a healthy asymptomatic carrier individual [12].

Patient Approach

Clinical Presentation

After an incubation period of 10–15 days, infants develop an abrupt high fever that can reach beyond 40 °C. This may last for 3–5 days, without other clear physical findings. The fever is followed by an abrupt defervescence that coincides with the development of the exanthem. During the febrile days, the infant can be active and well-appearing. Sometimes they may be irritable. Other clinical manifestations that have been reported during the febrile period include inflammation of the tympanic membranes, diarrhea, vomiting, bulging fontanelle, and an enanthem in two thirds of cases referred to as Nagayama spots, which are small red papules located on the soft palate and uvula.

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The skin rash that develops after the patient becomes afebrile is macular or maculopapular. It appears first on the trunk and neck and then spreads to the face and extremities. It is usually nonpruritic and lasts for 24–48 h.

Lab Investigations

Because of the lack of specific physical findings during the febrile phase, many infants undergo laboratory evaluation. Findings may include leukocytosis, leukopenia, atypical lymphocytosis, and thrombocytopenia. Pyuria can be observed, which can be confused with a urinary tract infection (UTI). However, urine culture is negative for bacterial growth.

Complications

Complications of roseola are uncommon, and most infants recover spontaneously without sequelae. However, they will continue intermittent shedding of the virus from body secretions for life. In individuals with immunocompromising conditions, reactivation of dormant HHV-6 can lead to encephalitis and cause graft-versus-host disease in liver or bone marrow transplant patients.

Treatment and Prevention

Treatment is supportive and may include antipyretics for the treatment of fever. As the transmission of HHV-6 often involves asymptomatic healthy individuals, prevention is difficult. No vaccine is available.

Erythema Infectiosum (Fifth Disease)

Erythema infectiosum (EI) is a mild self-limiting disease caused by Parvovirus B19 infection.

Epidemiology

EI mainly affects school-aged children and usually occurs in epidemics in winter and spring. Males and females are equally affected.

Patient Approach

Clinical Presentation

The virus is transmitted via respiratory droplets. After a 1–2-week incubation period, the child starts to have a nonspecific prodromal phase that manifests as fever, headache, sore throat, rhinorrhea, and arthralgia. Two to four days later, facial malar rash appears with circumoral pallor that gives patients the so-called "slapped-cheek appearance." Three to five days later a macular skin rash starts to appear on the trunk and extremities that lasts for few days and has a lacy-reticulated appearance as it starts to fade. After its resolution, the patient may experience recurrence of the rash in response to certain stimuli such as stress, exercise, and exposure to heat, a phase which can last for several weeks.

Complications

EI is mild self-limiting disease that usually resolves without complications in immunocompetent individuals. Aplastic crisis may occur in children with underlying hematologic abnormalities. Arthropathies are estimated to affect 10% of pediatric patients and up to 60% of adult patients [13].

Treatment and Prevention

Treatment is largely supportive and symptomatic. Isolation of affected individuals is not necessary as the rash is thought to be autoimmune in nature and the patient is no longer infectious when the exanthem appears.

Laryngotracheobronchitis

Definition and Background

Laryngotracheobronchitis, also known as croup, is a common viral infection affecting children under the age of 5 years. It primarily affects children between the age of 6 months and 3 years old. It is uncommonly seen among patients over 6 years of age.

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Epidemiology

Croup affects about 3% of children per year, and it accounts for about 7% of hospitalizations in the United States in children younger than 5 years of age. The main causative agent of croup is the parainfluenza virus (paramyxovirus family), primarily types 1 and 2, which cause 75% of cases. Other viral causes include influenza A and B, measles, adenovirus, and respiratory syncytial virus (RSV) [14]. In some circumstances, superimposed bacterial infections can follow viral croup.

Viruses causing acute infectious croup are spread through either direct inhalation from a cough and/or sneeze, or by contamination of hands from contact with fomites and subsequent touching the mucosa of the eyes, nose, and/or mouth.

Classification

Croup can be classified as mild, moderate, severe or life-threatening, according to the severity of the presenting symptoms (see Table 1). Hypoxemia is a very serious late sign and indicates life threatening croup.

Patient Approach

History

Like most other viral infections, the onset of cough and stridor is usually preceded by coryza and a low grade fever (38–39 °C) that can sometimes exceed 40 °C, and a cough. Within 1–2 days, the characteristic signs of hoarseness, barking cough, and inspiratory stridor develop, often suddenly, along with a variable degree of respiratory distress. Symptoms are perceived as worsening at night, with most emergency room visits occurring between the hours of 10 pm and 4 am. Symptoms typically resolve within 3–7 days but can last up to 2 weeks.

History of barking cough and stridor is usually gradual, with sudden increases in symptoms occurring at night. In cases of sudden onset stridor and cough, there should be consideration of the possibility of foreign body aspiration.

Physical Examination

Once croup is suspected, a physical examination should take place and should be carried out preferably while the child is calm to minimize work of breathing. The examination should start by inspecting the overall appearance of the child.

Regarding vitals, determining the respiratory rate is important, as is documenting temperature, pulse rate, and oxygenation. It is also essential to assess the hydration status of the patient, especially in infants.

Specific examinations of the respiratory system include observation of the use of accessory muscles for respiration, subcostal and intercostal retractions, and nasal flaring. The physical examination is key in the diagnosis and classification of the severity of croup and its subsequent management.

Table 1 Croup severity classification[a]

Item	Mild	Moderate	Severe
General behavior	Normal	Mild intermittent agitation	Drowsiness or severe agitation
Presence of stridor	Only with irritation or activity	Intermittent at rest	Continuous at rest
Signs of respiratory distress	None	Mild increase of accessory muscles, nasal flaring, and increased respiratory rate	Marked use of accessory muscles of respiration Increased or decreased respiratory rate (muscle fatigue)
Hypoxemia			Very late and serious sign indicates life threatening airway obstruction

[a]Adapted from several references and guidelines [17, 18]

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Lab and Imaging

Most of cases of croup do not require blood tests or imaging. However, in cases where the history and physical examination is not clear, or when there is a clinical suspicion of other diagnoses, neck or chest X-ray might be required. If lateral neck X-ray is obtained and the classic appearance, "steeple sign" (due to the narrowing of the subglottic area) may be seen, which supports the diagnosis of croup.

Differential Diagnosis

These include serious causes of acute stridor especially epiglottitis, foreign body inhalation, bacterial tracheitis, bronchiolitis, pneumonia, hyperreactive airway disease, or asthma.

Treatment

A recent Cochrane review concluded that croup score in children with mild to moderate croup does not improve greatly with inhalation of humidified air [15].

Medical treatment of croup depends on the assessment and severity of the case. In all cases parents should be counseled about the course of the disease and the red flags where urgent care should be sought.

In case of mild croup: the child is given oral steroids (one dose of dexamethasone 0.15–0.6 mg/kg or two doses of prednisolone 1 mg/kg, with the second dose given after 24 h of the first) and discharged, if patient is tolerating liquids. In the case of moderate croup; the child is given steroids (the same as for mild croup) and monitored for 4 h. If the child improves then she/he can be discharged. If the child does not show improvement or deteriorates then the patient should be managed as severe croup. In severe croup the child should be given oral or IM/IV dexamethasone of 0.6 mg/kg and be started on epinephrine nebulizers. Epinephrine should be given at the recommended dose of 0.05 mL per kg of racemic epinephrine 2.25% (maximum dose = 0.5 mL) or 0.5 mL/kg of L-epinephrine 1:1,000 via nebulizer (maximum dose = 5 mL). After administration of epinephrine nebulizer, the child should be monitored at least for 4 h, as rebound bronchoconstriction and edema can occur. After 4 h if the symptoms have resolved and the child has no accessory muscle use or stridor at rest, then the child can be discharged. If there is no or only partial improvement, then the child should be admitted to the hospital for further care. If at any point the child becomes hypoxemic then arrangements should be made for the child to be admitted to the pediatric intensive care unit without delay.

Epinephrine works via adrenergic stimulation, which causes constriction of the precapillary arterioles, thereby decreasing capillary hydrostatic pressure. This leads to fluid resorption from the interstitium and improvement in laryngeal mucosal edema [16].

Epiglottitis

Acute epiglottis is a life-threatening condition that should be considered when evaluating children with stridor. The prevalence of acute epiglottitis dramatically declined after the introduction of the *H. influenzae* vaccination. Epiglottitis usually occurs in children 2–7 years of age, with a peak incidence at 3 years of age. The classical presentation is with sudden onset of high fever and the child looks toxic and may be agitated. Respiratory efforts are usually increased with auditable stridor, dyspnea, muffled voice, dysphagia, and drooling. Sitting in a forward leaning (tripod) position with the mouth open and the tongue somewhat protruding might be observed in older children. The classical appearance of the "thumb sign" on lateral neck x-ray can be found in around 95% of cases [19], but once suspected, emergent referral to a higher level of care and preparation for airway management must be initiated without delay.

Acute Gastroenteritis in Children

Definition

Acute gastroenteritis is a clinical syndrome often defined by increased stool frequency (e.g., ≥3 loose or watery stools in 24 h or a number of

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loose/watery bowel movements that exceeds the child's usual number of daily bowel movements by two or more), with or without vomiting, fever, or abdominal pain [20].

Epidemiology

Gastroenteritis is the second leading cause of mortality among children between 1 and 59 months of age [21].

Pathogens causing gastroenteritis can be viral, bacterial, or parasitic; they are usually transmitted via the fecal-oral route. Viruses are the most common pathogens among children younger than 2 years, while bacterial and parasitic infections tend to affect older children and adults.

Rotavirus infection tends to occur in fall and winter. After the introduction of a rotavirus vaccine, norovirus is seen more commonly. Other viral causes of acute gastroenteritis include astrovirus, enteric adenovirus, and sapovirus. In most cases of acute gastroenteritis, diarrhea resolves within 1 week and vomiting within 1–2 days.

Bacterial gastroenteritis can occur following ingestion of poorly cooked meats, eggs, seafood, or unpasteurized milk. Clinically, patients tend to have more pronounced abdominal pain, high fever, and smaller stool volume compared to patients with viral gastroenteritis. In addition, they may have tenesmus and blood or mucus in the stool. Common bacterial causes include Enterotoxigenic *E. coli*, Enteroinvasive *E. coli*, Enterohemorrhagic *E. coli*, Salmonella, Shigella, Campylobacter, and *Clostridioides difficile*.

Differential Diagnosis

Gastroenteritis should be differentiated from other causes of diarrhea or vomiting such as systemic infections (e.g., pneumonia, urinary tract infection, meningitis, and otitis media), other viral infections like influenza and measles, diabetic ketoacidosis, and acute abdominal emergencies such as appendicitis and intussusception.

Clinical Evaluation

History and Physical Examination

History and physical examination should focus on the presence of symptoms of other causes of diarrhea and vomiting, recent contact with individuals with gastroenteritis, especially in the household or day care settings, food exposures, travelling abroad, or recent treatment with antibiotics. Hydration assessment is vital, caregivers should be asked about oral intake especially in the presence of vomiting, increased thirst, and reduced urine output. A more comprehensive evaluation of the hydration status may be elicited by physical examination (Table 2).

Table 2 Clinical features in infants and children with dehydration

Clinical feature	Mild (3–5%)	Moderate (5–10%)	Severe (>10%)
General appearance	Restless	Irritable, restless	Lethargic, unconscious
Tears	Normal	Normal or reduced	Absent
Eyes	Normal	Slightly sunken	Deeply sunken
Mucous membrane	Normal or slightly dry	Dry	Parched
Fluid intake	Thirsty	Thirsty, drinks eagerly	Drinks poorly
Skin turgor	Normal	Reduced (recoils in <2 s)	Reduced (recoils in >2 s), tenting
Capillary refill time	Normal (<2 s)	Delayed (>2 s)	Very delayed (>3 s)
Blood pressure	Normal	Normal to low	Hypotension
Pulse rate	Normal	Tachycardia	Tachycardia or bradycardia
Respiratory rate	Normal	Increased	Deep
Fontanelles	Normal	Depressed	Markedly depressed
Urine output	Normal or slightly reduced	Markedly reduced	Absent for several hours

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Lab Investigations

Stool studies (stool analysis, stool culture, and viral antigen detection) are indicated in cases of prolonged diarrhea beyond 7 days, in the presence of blood or mucus in stool, and in immunocompromised patients. Fecal leukocytes are frequently present in bacterial gastroenteritis. Electrolytes should be assessed in cases of severe dehydration to guide fluid management. In patients with suspected pseudomembranous colitis, a positive stool test for *Clostridioides difficile* toxin confirms the diagnosis.

Treatment

Management of acute gastroenteritis is largely supportive, with fluid management being the cornerstone. The use of antimotility agents in gastroenteritis is not recommended as they can prolong the course of bacterial diarrhea as they delay transit time. The use of adsorbents like smectites, a.k.a. diosmectite (brand names Smecta, Smecdral, Diosecta) can help reduce water loss and therefore can be considered for management of acute gastroenteritis [20]. Diosmectite is available in European countries, Asia, and Africa. Antiemetics are not recommended for routine use in the presence of vomiting as they can have serious adverse effects.

Fluid Management

Management of dehydration can be accomplished over three phases; deficit replacement, maintenance and ongoing losses replacement. The amount and type of fluids to be given during the deficit replacement phase depends on the degree of dehydration.

Oral Rehydration Therapy

Oral rehydration therapy (ORT) reduces childhood mortality from diarrheal disease. ORT is composed of water, glucose, and electrolytes. It can be given by parents or caregivers in both home and hospital settings without the need for intravenous access. ORS should be given in small amounts by spoon or syringe (5 mL every 1–2 min). The WHO and the UNICEF recommend a reduced-osmolarity formulation of ORT to avoid the risk of hypernatremia [22], with the ideal solution having a low osmolarity (210–250 mOsmol/L) and a sodium content of 50–60 mmol/L.

Deficit Replacement

Children manifesting no significant signs of dehydration who are considered to have mild dehydration (<5%) do not require deficit replacement. In patients with moderate (5–10%) dehydration, ORS are administered at a volume of 50–100 mL/kg over 4 h. In children with moderate dehydration, who cannot tolerate oral intake, a bolus of IV isotonic saline given as 10 mL/kg over 30–60 min can be used, followed by ORS to complete the deficit replacement.

Patients with >10% dehydration IV fluids are given initially as rapid infusion of 20–30 mL/kg of isotonic saline over 30 min to restore the circulation, followed by 70 mL/kg of isotonic saline over 2.5 h. As soon as the patient can tolerate oral intake, ORT should be initiated in addition to IVF, since most isotonic intravenous solutions replace water and Na but do not replace glucose, K, or other electrolyte losses. Replacement fluids should be continued under supervision until all the initial signs of dehydration are absent and the patient has urinated. This may require more fluids than initially estimated.

Maintenance Fluids and Ongoing Losses

Once repletion has been completed patients should be started on maintenance fluids given as ORS and feeding should be resumed. In addition, children who manifest no signs of dehydration at presentation can be sent home safely with ORS maintenance treatment. Maintenance fluids are calculated based on patient's weight according to the Holliday-Segar method (100 mL/kg for the initial 10 kg body weight, 50 mL/kg for the second 10 kg of body weight, and 20 mL/kg for the rest of their body weight) given over 24 h. During both the deficit replacement and maintenance phases, ongoing losses by emesis or diarrhea should be estimated as 10 mL/kg for each episode

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of diarrhea and 2 mL/kg for each episode of emesis. These losses should be added to the amount of fluids to be given in the next hour.

Nutrition and Zinc Supplements

Children with acute gastroenteritis should be encouraged to start solid foods as soon as oral intake is tolerated and in infants, breastfeeding or undiluted formula intake continues during the deficit replacement phase as well as during the maintenance phase. During the refeeding process, complex carbohydrates, vegetables, fruits, lean meats, and yogurt are usually tolerated, while fatty foods and foods rich in sugars should be avoided as they can increase diarrhea. The WHO recommends oral zinc sulfate for children under 5 years of age with infectious diarrhea (10 mg/day for children under 6 months and 20 mg/day for children 6 months to 5 years, each for 10–14 days), to reduce the severity and duration of diarrhea and reduce the incidence of subsequent episodes of diarrhea for several months [23].

Antibiotics

Antibiotics are not indicated for most children with acute watery diarrhea, except in patients with suspected cholera, in which case macrolides, fluoroquinolones, and tetracyclines are possible options. Azithromycin, ciprofloxacin, and cefixime can be considered empirically in severe cases of bloody diarrhea while awaiting stool culture results. Antibacterial agents should be avoided when enterohemorrhagic *E. coli* infection is clinically suspected to avoid increasing the risk of hemolytic uremic syndrome. Table 3 summarizes antimicrobial agents for common pathogens causing bloody diarrhea, following the result of stool culture.

Probiotics

Several studies that have been conducted on probiotics in pediatric patients with acute bacterial diarrhea found that probiotics (like *Lactobacillus rhamnosus GG*, *Saccharomyces boulardii*, and *Lactobacillus reuteri*) may be effective in reducing duration and severity of symptoms [24].

Prevention and Vaccination

Acute gastroenteritis can be prevented by meticulous public and personal hygiene especially in childcare facilities. Thorough cooking of meats and poultry are recommended as well as avoidance of unpasteurized milk. Breastfeeding should be encouraged. Breast milk is rich in antibodies and other factors protective against gastroenteritis. Vaccines to prevent rotavirus and hepatitis A infections are recommended. Rotavirus vaccine is an orally administered live virus vaccine that is given in two or three doses depending on the specific vaccine administered.

Kawasaki Disease

Definition/Background

Kawasaki disease (KD) is a systemic vasculitis affecting small- and medium-sized blood vessels and it is considered the leading cause of acquired heart disease in industrialized countries [25].

Epidemiology

The estimated incidence of KD in North America is ≈25 cases per 100,000 children [26]. The highest incidence is reported in Japan where incidence can reach 243.1 per 100,000 population aged 0–4 years. This disease has a ratio of males to females of ≈1.5:1 [27].

History and Physical Examination

Typically, children with KD are less than 5 years old, but older children and rarely adolescents can be affected. KD is characterized by persistent fever for at least 5 days. In the absence of appropriate therapy, fever can continue for 1–3 weeks [28].

Parents might describe redness and painful swelling on the palms and soles of affected children. After 2–3 weeks desquamation of the fingers and toes takes place, which might extend

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Table 3 Oral antimicrobial agents for bloody diarrhea in children based on infecting organism

		Drug	Dose and administration	Duration	Notes
Shigella		Azithromycin	12mg/kg day 1 followed by 6 mg/kg daily for days 2–5	5 days	
		Cefixime	8 mg/kg/day QD or BID	5 days	
		TMP-SMX	8–10 mg/kg (based upon TMP component) BID	5 days	If isolated strain is susceptible
Salmonella (nontyphoidal)		TMP-SMX	8–10 mg/kg BID	7–10 days	Their use should be preserved for young infants, infants with high fever and immunocompromised children
		Cefixime	8 mg/kg/day QD or BID	7–10 days	
		Azithromycin	15 mg/kg day 1 followed by 10 mg/kg daily days 2–5	5 days	
Campylobacter		Azithromycin	15 mg/kg day 1 followed by 10 mg/kg daily days 2–5	5 days	Effective if started in the first 3 days of disease onset
Entamoeba trophozoites		Metronidazole	35–50 mg/kg/day TID	7–10 days	
Giardia		Metronidazole	15 mg/kg/day TID	5–7 days	
Clostridioides Difficile	Mild to moderate	Metronidazole	30 mg/kg/day QID	7–14 days	
	Severe or recurrent	Vancomycin	40 mg/kg/day QID	10 days	
		Fidaxomicin	200 mg BID	10 days	For children >6 years

to palms and soles, and a couple of months later Beau's lines (deep transverse grooves across the nails) might be noticed [25, 27].

The morphology of rash in KD may vary. While diffuse maculopapular eruption is most common, scarlatiniform rash, erythroderma, or erythema multiforme-like rashes are also seen. Less frequently urticarial rash can occur [26]. An unusually severe form of psoriasis with plaques and pustular features can rarely occur during or after the acute KD illness [29]. Patients also experience bilateral bulbar nonexudative conjunctival injection which usually begins shortly after the onset of fever and often spares the limbus. Anterior uveitis may be observed by slit-lamp examination during the first week of fever.

Signs and symptoms in the lips and oral cavity include erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips; a "strawberry tongue," with erythema and prominent fungiform papillae; and diffuse erythema of the oropharyngeal mucosa.

Cervical lymphadenopathy is the least common clinical feature. Lymph node swelling is usually unilateral, $\geq$1.5 cm in diameter, and confined to the anterior cervical triangle [30]. In a small subset of patients, lymph node findings may be the most notable and sometimes they are the only initial clinical finding, prompting a clinical diagnosis of bacterial lymphadenitis, and significantly delaying KD diagnosis [30].

There is no specific test for KD. The diagnosis is a clinical one [26].

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Classic KD is diagnosed in the presence of fever for at least 5 days (the day of fever onset is taken as the first day of fever) together with at least four of the five following principal clinical features:

1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy ($\geq$1.5 cm diameter), usually unilateral

However, patients may not exhibit four or more clinical features at once, rendering diagnosis difficult. For example, some patients may present with fever and meet two or three of the classic criteria. These patients are considered to have incomplete KD [28].

Laboratory and Imaging

As mentioned above, the diagnosis of KD is a clinical one. However, initial laboratory evaluation may be required when the clinical presentation does not meet the full criteria of complete KD and it may include a complete blood count (CBC), electrolyte panel, renal function testing, liver enzymes, albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and urinalysis. Abnormal limits include Albumin 3 g/dL or less, anemia for age, elevated ALT levels, platelets >450,000, WBC count 15,000/mm^3 or greater, and sterile pyuria. Three or more positive laboratory criteria are supportive of a diagnosis of KD.

Echocardiography should be performed to evaluate for coronary artery abnormalities or involvement during the acute stage and it should be repeated at 1–2 weeks and then 5–6 weeks after disease onset. Transthoracic echocardiography is the diagnostic imaging modality of choice to screen for coronary aneurysms. MRI and MRA may be used to image peripheral artery aneurysms.

Cardiac stress testing for reversible ischemia is indicated to assess the existence and functional consequences of coronary artery abnormalities in children with Kawasaki disease and coronary aneurysms.

Treatment

The goal of therapy in the acute phase of KD is to reduce inflammation and arterial damage and to prevent thrombosis in patients with coronary artery abnormalities. The mainstay of initial treatment for both complete and incomplete KD is a single high dose of IVIG together with acetylsalicylic acid (ASA). IVIG should be instituted as early as possible within the first 10 days of illness marked by the onset of fever. Referral to specialized care is warranted once KD is suspected [26, 31].

Medications\Immunizations and Chemoprophylaxis, Referrals, and Counseling

Current long-term management protocols are calibrated to the degree of coronary artery involvement reflecting the known likelihood of severe long-term cardiac complications. Therefore, patients are managed according to risk category [32].

Patient Education and Activation

Since affected children are at risk of complications throughout their lives, parents should be educated to help their children adopt a healthy lifestyle and to avoid cardiovascular risk factors, including obesity, high-fat/high-calorie diets, sedentary lifestyle, alcohol use, and tobacco use, to limit their already high cardiac risk.

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Prevention

There are no known preventive measures for Kawasaki disease. Approximately one patient in every hundred cases may develop a recurrence. Parents should be counseled that there is nothing they could have done to prevent the disease.

Pinworms

Epidemiology

Pinworm infestation is one of the most common parasitic infections seen by family physicians. The infection is caused by a small, thin, white roundworm called *Enterobius vermicularis*. Of all age groups, school aged children are most at risk for pinworm infections, particularly those who live in close, crowded conditions [31].

Transmission

E. vermicularis is transmitted via the fecal oral route. The cycle begins when the gravid adult female worms lay their eggs on the perianal folds. Scratching of the perianal area then leads to autoinfection by transfer of infective eggs to the mouth. Following ingestion, it takes about 1–2 months for the gravid adult female to mature and migrate to the colon where it lays eggs around the anus at night. Each female worm can produce 10,000 or more eggs. Since humans are the only natural host, person-to-person transmission can occur by eating food touched by contaminated hands or by handling contaminated clothes or bed linens or through contact with environmental surfaces that are contaminated with eggs. In addition, eggs may become airborne, inhaled, and swallowed.

Clinical Presentation and Diagnosis

History and Physical Examination

Affected children usually present with complaints of anal itching, also known as pruritus ani, which is most severe at nighttime or in the early morning. Pinworms can also cause vulvar symptoms, such as itching. Children with recurrent episodes of vulvar itching, especially at night, should be examined for pinworms. The worm count might get so high that abdominal pain, nausea, and vomiting develop. Most patients, however, are asymptomatic. Pinworms have also been linked to appendicitis and Eosinophilic enterocolitis. Adult pinworms may be found in normal and inflamed appendices following surgical removal. Urinary tract infections have also been described in young girls with pinworms.

Laboratory and Imaging

The female pinworm (10 mm) can be seen in the perianal region with the naked eye so parents can simply look for the worms in the perianal region 2–3 h after the child wakes from sleep. Alternative techniques such as the "scotch tape test" and analyzing samples from under the fingernails under a microscope can aid in the diagnosis. The "scotch tape test" involves the use of a transparent tape which is applied to the perianal area to collect possible pinworm eggs around the anus first thing in the morning. If a person is infected, the eggs on the tape will be visible under a microscope. The tape method should be conducted on three consecutive mornings right after the infected person wakes up and before he/she bathes or washes the perianal area [31, 33].

Treatment

It is important to simultaneously treat the entire household for pinworms when a decision is made to treat. Anthelmintics, such as mebendazole (100 mg PO as a single dose), pyrantel pamoate (11 mg (base)/kg PO not to exceed 1 g/dose), and albendazole (400 mg PO × 1), are active against *Enterobius vermicularis*. Any of these drugs are given as a single initial dose, and then another single dose of the same drug is given 2 weeks later to prevent re-infection by adult worms that hatch from eggs not killed by the first treatment [31, 33].

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Prevention

Children should be encouraged to wash their hands with soap and warm water after using the toilet and bathe every morning to help reduce the number of eggs on the skin. In institutions, day care centers, and schools, control of pinworm infections can be difficult, but mass drug administration during an outbreak can be successful [31].

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Behavioral Problems of Children

18

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General Principles

Behavioral problems in children are both common and underdiagnosed [1, 2]. While some of these conditions have prominent genetic or neurological contributions, it is now widely appreciated that most behavioral problems in children result from maladaptive responses to their environment. Stress, parenting issues, and family environment contribute to behavioral problems [3]. Although many may dismiss childhood behavioral problems as being benign and temporary, studies show that most adult mental health disorders first manifest in childhood, often arising from a preexisting behavioral problem [4]. The family physician plays an essential role in the early detection and treatment of childhood behavioral problems and can reduce both childhood and adult morbidity by detecting these conditions and ensuring early intervention [5].

Attention Deficit Hyperactivity Disorder

Epidemiology

ADHD is the most common childhood neurobehavioral disorder. It is a neurodevelopmental disorder that manifests with symptoms of hyperactivity, inattention, and poor impulse control. US epidemiologic data report that 7–11% of children in the United States are diagnosed with ADHD and the majority of these children are treated with psychostimulants [6]. Data from other countries suggest a similar prevalence internationally.

ADHD is thought to result from delayed maturation of some executive brain functions. Both genetic and environmental causes are thought to contribute to the genesis of the syndrome. The observation of both strong familial clustering and apparent vertical transmission can be the result of both genetic and environmental factors. Functional neuroimaging studies have also shown significant differences between children with ADHD and more typically developing peers [7].

Diagnostic Considerations [8]

The diagnosis of ADHD should be considered in a child presenting with hyperactivity and impulsivity that are not appropriate for their developmental stage. Additionally, the behaviors are pervasive in most environments in which the child functions. These behaviors should also interfere with his or her areas of function, specifically learning, peer relations, and relationships with adults and authority. Most children present with these symptoms during early school years when the demands on their compliance with instructions and attention increase. However, an increasing number of younger children under 4 years of age are being diagnosed with ADHD. Boys are more commonly affected than girls in the hyperactive and combined type, while more girls are affected more often with the predominantly inattentive subgroup

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of ADHD. Establishing the diagnosis depends on fulfilling the DSM-V diagnostic criteria, which in part require the behavior reported to be observed in multiple settings.

The Vanderbilt ADHD Diagnostic Rating Scale can facilitate the diagnosis in the primary care setting. Parent and a teacher forms are available for initial diagnosis and follow-up on treatment effectiveness. The questionnaire is self-administered by the parent and the teacher and includes scoring instructions. The instrument is available on the Internet for use free of charge. It has also been translated and validated in many languages. The use of an instrument has advantages in both documenting the diagnosis and also increasing parental awareness of what behaviors may constitute symptoms of ADHD.

At the time of diagnosis, it is important to consider other conditions that can mimic the presentation of ADHD or coexist with it as a comorbid condition. Common among these are learning disabilities. Difficulty learning and its resultant frustration can result in secondary maladaptive behaviors. Oppositional behavior can present with symptoms similar to ADHD. Oppositional disorder, anxiety, and depression are common comorbidities that are also screened in the Vanderbilt. A low threshold for diagnosis of these conditions in children with ADHD should be maintained. Comorbid conditions often influence the diagnosis and management.

Treatment of ADHD

Both behavioral and pharmacological treatments are effective in the treatment of patients with ADHD [8]. A combination of behavioral and pharmacological interventions often has a beneficially synergistic effect. The choice of approach chosen depends on factors such as the age of the child, the urgency of symptoms, quality, and availability of referral sources and family factors. Family factors include how functional and organized the family is, as well as family's attitudes and preferences toward the use of medications. In younger children, those less than less than 4–5 years of age, behavioral approaches are typically the first-line treatment. However, pharmacological treatments have a faster onset of action and can result in almost immediate symptomatic improvement of the core symptoms of ADHD for older children. Pharmacologic management is most useful in situations where symptoms are severe and causing a lot of disruption.

Pharmacological Treatments

The use of psychostimulants has been shown to be safe and effective in the treatment of ADHD in children [9]. Stimulant medications result in improvement of the core symptoms of ADHD and allow better social functioning. Although psychostimulants do not to "cure" attentional and hyperactivity problems, over the long term, many people develop strategies to better manage these problems as they mature.

Several psychostimulant preparations are available and FDA approved to treat ADHD. Approved nonstimulant options are available and are typically used if there is a poor response to stimulants, concern for diversion or abuse, side effects, or patient preference.

Following are ten general principles for the treatment of ADHD with psychostimulants:

Before you start:

1. A complete history and physical examination with special attention to a history of heart disease, careful blood pressure measurement, and full neurological examination. Laboratory testing is not generally required unless these are indicated by findings on the history and physical examination.
2. Parent and patient should be counseled about the side effects of the medication including appetite suppression. Also this is a good time to make a referral to behavior therapy and/or to counsel the parent on behavioral modifications at home.
3. It is recommended that the parent inform the child's teacher and school nurse that medication is being initiated.

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When you prescribe:

4. Start with an initial low dose and increase gradually as required and tolerated.
5. The morning dose can be taken after breakfast if appetite suppression is a concern.
6. Start with a short acting preparation and move to a long acting preparation if needed once the efficacy and tolerance of the medication is established.
7. Increase the medication dose as needed to control symptoms until the maximum recommended dose is reached or the patient has side effects.
8. Medication administration should be supervised by parents. Parents and patient should be counseled about the potential for abuse and diversion. The exact number of tablets is to be dispensed on a monthly basis. A controlled substance license is required for prescribing psychostimulants. Refills of more than a 1-month supply are generally not allowed.

Follow-up and monitoring

9. Monitor closely at the beginning of treatment. It is advisable to bring the patient and parent in for a follow-up visit in 1 week after starting the medication and after every dose change, to check for tolerance, side effects, blood pressure, and score symptom control. Once a stable dose is achieved, follow-up every 6 months is recommended for monitoring of growth, blood pressure, symptoms, and side effects.
10. Switching to another agent may sometimes be helpful if the maximum dose is achieved without desired clinical improvement or side effects are observed. The second agent should also be started at a low dose and increased gradually.

Management of suboptimal or no response to treatment:

Several issues need to be considered in cases of a lack of response or a suboptimal response. These include:

- Patient is not receiving the medicine: consider whether this is because of lack of organization or because the medication is being diverted.
- Unstructured or chaotic family environment, including domestic violence, homelessness, child maltreatment, or other environmental stressor.
- Wrong diagnosis or unaddressed comorbidity. Common comorbidities include posttraumatic stress disorder, learning disability, anxiety, and severe environmental or psychosocial adversity such as domestic violence, child abuse, or neglect.

Behavioral Treatments for ADHD

Two types of behavioral management are used for patients with ADHD.

1. General behavioral management and environmental modification: this can be very helpful in improving function. For example, establishing a clear and structured routine. Management checklists can be very helpful. One on one attention and behavioral reinforcement by the parents is effective in modifying behavior.
2. Cognitive behavioral therapy can be used in older children and adolescents to internally restructure behaviors. This is generally accomplished through therapy sessions with a psychologist trained in this form of therapy.

Consider referral to a psychiatrist or subspecialty developmental pediatrician:

1. Lack of response to the usual first or second line medications
2. Concern about complex psychiatric or other specific comorbidity

Learning Disabilities, Specific Learning Disorders, and Learning Difficulties

General Principles

"Learning disability" is a legal term used to describe the learning difficulties that result from Specific Learning Disorders (SLD). Learning difficulties and poor academic progress can

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result from many causes [10]. These include inadequate instruction, untreated attentional problems, or physical problems such as vision or hearing problems. Academic achievement in a second language may be difficult for immigrants and refugees who may also have other risk factors for poor academic performance including interrupted schooling and the psychosocial impacts associated with war or displacement.

Specific Learning Disorders (SLD)

These are a group of cognitive disorders that interfere with learning and the use of academic skills, resulting in poor academic performance that is not congruent with the child's cognitive abilities. By definition, these children do not have intellectual disability, global developmental delay, or any other neurological or neurodevelopmental disorder that can account for the learning deficits. SLD are developmental disorders and are present from the onset of formal academic learning, when the child enters school. However, they may not manifest until the demands for learning and academic skills exceeds the child's ability or his or her compensatory mechanisms. These might include excessive effort or high levels of external support.

Three types of SLD are described in the DSM-5 depending on the specific area of impairment. Those are: impairment in reading, impairment in written expression, and impairment in mathematics. Additionally, the degree of deficit varies between individuals. The DSM-5 classifies the severity of SLD from mild to severe depending on the effectiveness of remediations that result in functional learning.

Diagnosis of Specific Learning Disorders

Learning and academic achievement are distributed along a continuum. Therefore, there is no specific cut point that defines a person as having SLD. The diagnosis is made based on arbitrary criteria that depend on established societal norms and expectations.

Learning disorders should be suspected in any child whose academic achievement is below the expected range for age and class. Establishing the diagnosis of SLD requires a comprehensive evaluation that includes:

1. A complete history and physical examination including a complete neurological assessment, developmental and family history.
2. History of the educational difficulty including school reports and formal assessments.
3. Assessment of social functioning.
4. If available, formal psychometric testing that establishes normal cognitive function in addition to a formal educational assessment demonstrating below-average performance on academic achievement skills.
5. Evaluation of comorbidities including attentional deficits or behavioral problems.

If the assessment indicates the possibility of an underlying condition that may contribute to the learning difficulty, it should be investigated accordingly and ruled in or out.

Management of the Child with SLD

1. The first step in the management is counseling the child and family about the condition and what to expect. This is important and can help the child and family adjust to the condition and prevent problems arising from unrealistic expectations for the future.
2. In the United States, children with SLD are eligible for special education resources through the school system based on the Individuals with Disabilities in Education Act. Coordination with the school system is important for optimal outcomes of these children.
3. Utilization of a "strengths based approach" empowers the family and the child to find an area of strength in which the child can succeed while pursuing strengthening of their deficits. Children with SLD have IQs in the normal range by definition and therefore may be able

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to do well in areas that do not depend heavily on (for example) reading or math. These might include sports, art, specific technical skills, and so forth. This approach allows the child to have an opportunity to succeed and perhaps excel in other areas. This in turn helps with self-esteem and emotional health.

4. Children with SLD are at higher risk for secondary behavioral and emotional difficulties. Prevention, early detection, and proper management and referral as needed for these conditions can improve the outcomes of children with SLD.

Disruptive, Impulse Control, and Conduct Disorders

General Principles

Several diagnostic entities that fall under this general heading are described in the DSM-5. These include oppositional defiant disorder, conduct disorder, intermittent explosive disorder, antisocial personality, pyromania, and kleptomania. It has been proposed that these conditions be termed "behavioral addictions." This is in recognition that these disorders appear to share the core features of other kinds of addictions, specifically craving and loss of control. These diagnoses are also linked by the fact that the behaviors result in harm to the sufferer and/or others. Children are diagnosed with these disorders when the observed disruptive behaviors are severe, pervasive, and cause problems or distress [11].

Diagnostic Considerations

Oppositional defiant disorder is persistently hostile, disrespectful, and disobedient behavior usually directed at authority figures, such as parents or teachers. *Conduct disorder* is a pattern of aggression toward others that may include destruction of property and physical violence. In children, *intermittent explosive disorder* may present as severe, repeated tantrums that are out of proportion to the stressor. In older individuals, there is a pattern of brief (usually less than 30 min) angry outbursts that may or may not be accompanied by physical aggression or property destruction. *Antisocial personality* is a habitual disregard for the feelings, safety, or rights of others.

Conditions that are commonly comorbid with these disorders are attention deficit/hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety, and depression.

The complete criteria for diagnosing these conditions are found in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [12].

Treatment

Treatment of these conditions is focused on improving the patient's quality of life, reducing the harms caused by behaviors, and inhibiting the progression of these conditions to more serious forms of disordered behavior as the child becomes older. The treatment of these disorders is dependent on the age of the child, the severity of the symptoms, the degree of insight that the sufferer has into the behaviors in question, and their motivation to improve. Behavioral treatment may be appropriate for young children with milder symptoms. In older motivated individuals with insight, cognitive behavioral therapy is favored. Parent training and family therapy are also important adjuncts to these therapies.

In children who are not good candidates for cognitive behavioral or other behavioral interventions, psychotropic medications have been used. Psychotropics are also used to treat comorbidities that may be present. These include some SSRIs, anticonvulsants, stimulants, and atypical antipsychotics, but discussion of specific treatments are beyond the scope of this chapter.

Anxiety and Specific Phobias

Childhood and adolescence are considered to be a time of heightened risk for the development of anxiety disorders [13]. Studies report that most

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anxiety disorders have their onset in childhood. Anxiety disorders are thought to be the most common mental disorders in childhood. Several specific anxiety syndromes are described in the DSM-5. Separation Anxiety Disorder and Specific Phobias are the two most common entities in childhood. Diagnosing anxiety disorders in primary care may be challenging for several reasons. Younger children may not have achieved the developmental skills that allow them to recognize, verbalize, or process their feelings so they may not be able to describe what they feel. Therefore, the evaluation depends on adult reports which may be biased in a number of ways. Additionally, core symptoms of anxiety differ with age and developmental stage which may add a level of complexity when interpreting criteria for diagnosis and the results of assessment tools.

Risk factors for the development of anxiety in children include a family history of anxiety disorders. Other associations include cold, overprotective, or authoritarian parenting styles.

Screening instruments that help the clinician to detect anxiety include the GAD 7 and SCARED [14].

Diagnostic Considerations

Assessment of children with anxious symptoms requires a detailed history and physical examination. The interview should include the onset and evolution of the anxious symptoms, aggravating and alleviating factors, as well as a family history. In addition, associated symptoms are elicited. Evaluation of the family including parental mental health and home relationships, parenting styles, and economic status are important. Attention to detail and time are needed to make sure the age-appropriate criteria are met for the diagnosis.

Treatment

Referral should be considered if the presumed anxiety symptoms are causing significant disruption of function, especially in younger children. For older children, Cognitive Behavioral Therapy (CBT) has been shown to be effective when administered by a trained therapist [15]. In addition, several serotonin and serotonin norepinephrine reuptake inhibitors have been shown to be effective in treating children with anxiety. Detailed discussion of the pharmacologic treatment for children with anxiety is beyond the scope of this text.

Tics

Tics are a neurobehavioral condition that has its onset before 18 years of age. Tics are defined as sudden, rapid, repetitive, recurrent non-rhythmic movement or vocalizations.

Although tics are involuntary movements, they can often be suppressed voluntarily but only temporarily. The most common types of tics are blinking and throat clearing, but almost any muscle group can be involved.

Tics can occur as part of a specific tic syndrome such as Tourette syndrome, or they can be associated with another CNS disorder. More commonly, they occur in isolation and in the absence of any known medical or neurological disorder. Sometimes, it occurs as a sequela of a streptococcal infection (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS); see ▶ Chap. 20, “Selected Problems of Infancy and Childhood”).

Isolated tics are usually transient, but can be chronic. They are common in childhood, with a peak onset at 4–6 years of age. Boys are affected more commonly (M:F ratio of 2–4:1).

Chronic persistent tics are diagnosed when a person has had tics for over a 12-month period even if he or she had remissions (or tic-free periods) during this time.

Children who have tics have a higher risk of comorbid behavioral conditions including ADHD, OCD, and separation anxiety. These conditions often have a greater impact on the patient’s function than tics do.

Adult onset tics are rare. Adult presentations of tics are usually secondary to CNS insults

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or intoxication with a substance and an evaluation to rule out these conditions is warranted. Not uncommonly adults present with mild and undiagnosed tics in childhood that only become clinically significant in adulthood.

Diagnostic Considerations

In addition to a thorough history and physical examination, evaluation for comorbid conditions in children is recommended. These include OCD and other anxiety disorders, ODD and ADHD. In children with an abrupt onset of tics streptococcal throat culture, antistreptolysin-O (ASO) and antiDNAse-B (ADB) serum titers may be considered.

Management of Tics

Counseling patients and parents about the natural history of tics and the benign nature of childhood tics combined with watchful waiting is an acceptable option in individuals who do not experience functional impairment. In more severe cases, especially with children older than 9 years of age, the patient may be referred for behavioral therapy. Comprehensive Behavioral Intervention for Tics (CBIT) combines several behavioral therapeutic approaches to address tics and has been shown to be effective and is considered to be the first line of treatment should treatment be required.

Several medications have been studied for the treatment of tics. Two alpha 2 agonists clonidine and guanfacine have been shown to reduce the tic severity in placebo-controlled trials. In children who have comorbid ADHD, these two medications can also help reduce ADHD symptoms. Other classes of medications have been studied for the treatment of tics. These include antipsychotics, antiepileptics, and botulinum toxin; however, treatment with these agents is associated with a higher risk of adverse effects, so this limits their usefulness in the primary care setting [16].

Thumb Sucking

Thumb sucking and finger sucking is a universal phenomenon among children. Usually, persistent thumb sucking resolves spontaneously between 2 and 4 years of age. Negative effects of thumb sucking include paronychia, koilonychias, and most importantly dental malocclusion. Educating the caregivers in positive and negative reinforcement for this behavior is usually sufficient for treatment. Fingernail lacquer that has a noxious taste can be used ("Thum" Liquid). If the habit is recalcitrant to behavioral interventions and there is concern for the development of dental malocclusion (especially after age 4), referral to a pediatric dentist for consideration of preventive orthodontic devices may be helpful.

Pica

General Principles

Pica is defined as the craving and ingestion of non-food substances. These might include dirt, chalk, or paint chips. It is classified under the section on eating disorders in the DSM-5 and considered along with rumination disorder.

In most situations, pica is a transient condition and subsides with little or no intervention other than active supervision. In some patients, it may be a symptom of nutritional deficiency such as iron or zinc deficiency.

Pica increases the risk of lead or other toxic poisoning, as well as enteric infections involving bacteria or parasites. Pica is more common among children who suffer from intellectual disability. Other conditions reported to be associated with a higher risk of pica include pregnancy, sickle cell anemia, and renal failure [17].

Diagnostic Considerations

The evaluation of children with pica should include screening for iron and zinc deficiency and evaluation for developmental and

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behavioral conditions such as developmental delay, intellectual disability, and autism. Evaluation might include screening for lead poisoning and other conditions based on clinical suspicion.

Management

Behavioral modification strategies that might include distraction, reinforcement, and reward may be helpful and may be all that is needed for resolution of the behavior in most children.

Temper Tantrums

General Principles

Temper tantrums are normal developmental behavior for toddlers, and most are easily manageable. Inadvertent rewarding of the behavior may cause tantrums to escalate and become more disruptive. This happens when the child receives positive or negative attention when he/she throws a tantrum. In most cases, counseling parents to increase nurturing behaviors when the child is exhibiting normal behavior, ignoring minor misbehaviors and tantrums, and teaching them "time out" techniques is usually helpful and effective.

Diagnostic Considerations

Evaluation of the child with difficult-to-manage temper tantrums must include a detailed history including a family history, social history, parenting practices, and an assessment of family dynamics. A mother suffering from depression may not be able to provide responsive parenting and may become overwhelmed with the task of managing her toddler's behaviors. A complete developmental evaluation and physical examination is also essential to rule out developmental delays or atypical development. Referral for further evaluation may be needed in some cases.

Management and Prevention

Positive parenting and a nurturing responsive environment and caregivers are shown to foster the development of healthy emotional regulation in children and can prevent the development of maladaptive behaviors such as temper tantrums [18].

Parenting training and instruction in behavioral modification are usually effective and sufficient for management of this problem. Children suffering from conditions such as autism and global developmental delay have may have particular difficulty in regulating their emotions and a referral for behavioral modification may be helpful in these cases.

Sleep Disturbances

General Principles

Most sleep disturbances in infants and young children are the result of inadvertently reinforcing behaviors that disrupt sleep. These include rocking the baby to sleep or associating sleep with the presence of the adult caregiver, which means that when the child inevitably wakes up in the middle of the night they cannot put themselves back to sleep. They then have to call the parent to help them go back to sleep. In older children and adolescents, the use and exposure to digital screen media has been recently linked to sleep disruption [19].

Management

Management of night awakening depends on the age of the child. In infants the technique of "modified extinction" is effective. It is also acceptable to most parents and is relatively easy to do. The parents are instructed to establish a bedtime routine. Sleep hygiene including a bed time routine that would include regular bedtime, a winding down time, getting ready for bed rituals such as brushing teeth, bathing, and putting pajamas on, followed by quiet activities such as reading a book

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or telling stories or bedtime songs. The child should then be allowed to fall asleep in their bed, on their own. If the child won't sleep and cries when left in the crib, the parent should go back to the room every 5–10 min to reassure the child without picking him up then go back out of the room. This will take longer than the "unmodified extinction" method in which the parent does not go back in the room allowing the child to "cry it out" and eventually fall asleep. Unmodified extinction works faster but is usually more difficult for the parents to comply with.

In toddlers, the child can get out of the bed and go into the parents' room. The parents should take him back to his room promptly every time he does that, and eventually the child will learn to stay in bed. The parents also can use a sticker chart with positive reinforcement as well as strategies to make it less scary for the child to stay in his room such as having a night light, a cuddly toy, or a special blanket.

In older children, the use of screens by children and adolescents can potentially cause sleep disruption especially if used in the evening. The bright light disrupts the natural production of melatonin which helps with sleep. Additionally, stimulating content such as action movies or games may disrupt the normal transition to sleep [20]. Parents should be advised to supervise the content as well as total duration of screen time as well as enforcing turning off all screens including television and cell phones at least 2 h before bedtime [21].

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Musculoskeletal Problems of Children 19

Christine Q. Nguyen, Carolina S. Paredes-Molina, Trista Kleppin, Teresa Cvengros, and George G. A. Pujalte

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Most family physicians see many musculoskeletal complaints in their office, but they should be aware that children have some conditions that are unique and may not be encountered in adults. This chapter will discuss generalized and regional musculoskeletal conditions, including fracture patterns, gait concerns, and overuse issues encountered among children and adolescents.

Generalized Musculoskeletal Conditions

Common Fracture Patterns

Physeal Fractures

Fractures involving the growth plate of children are called "physeal fractures." These need to be managed with care because they may result in premature closure of the growth plate. Typically, these injuries occur in girls 11–12 years

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old and boys 13–14 years of age, but more commonly in boys (2:1 ratio), with fractures of the distal radius, distal tibia, and distal fibula being the most common [1]. Physeal fractures are usually diagnosed using plain radiographs, often with the help of comparison x-rays of the non-affected limb. They are generally categorized according to the Salter-Harris classification [2] (Fig. 1). A useful mnemonic is [3]:

- S ("Straight across") – Type I
- A ("Above") – Type II
- L ("Lower" or "BeLow") – Type III
- T ("Two" or "Through") – Type IV
- E ("End") or ER ("ERasure of the growth plate") – Type V

Management will depend upon the location of the fracture, but, generally, all types are managed in consultation with orthopedic specialists. The lower numbered Salter-Harris fractures tend to have fewer complications and better outcomes. A nondisplaced Type I or II fracture is usually immobilized and casted. However, if they are displaced, they will need reduction within 1 week of the injury, followed by immobilization with casting for 3–4 weeks. Salter-Harris Types III–V need prompt orthopedic evaluation because they usually require open reduction. Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually used for pain management, although there are studies that indicate that acetaminophen may be better, as NSAIDs have been shown to be detrimental to bone healing.

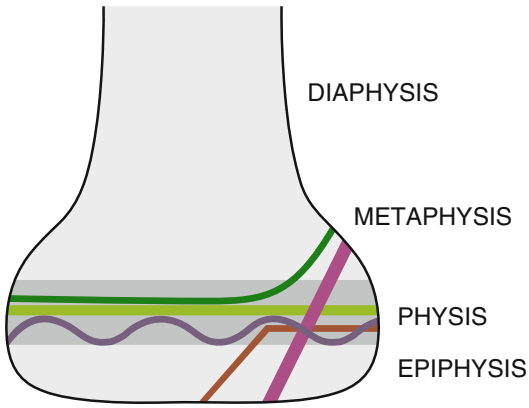


Fig. 1 Salter-Harris classification is defined by the location of the fracture relative to the growth plate (*the gray zone*). Type 1 (*yellow*) is a separation of the growth plate (*STRAIGHT across*). Type 2 (*green*) is a fracture ABOVE the growth plate into the metaphysis. Type 3 (*orange*) is a fracture that extends LOWER than the growth plate into the epiphysis. Type 4 (*pink*) is a fracture that extends THROUGH the epiphysis, physis, and metaphysis. Type 5 (*purple*) is a fracture that ERASES the growth plate due to compression injury. (Image adapted from mnemonic, which was reprinted from Ref. [3], Copyright (1999), with permission from Elsevier)

Buckle Fractures

Buckle fractures are sometimes referred to as "torus fractures." These fractures result from longitudinal compression, such as that which occurs when one falls on an outstretched hand. The bony cortex does not actually break [1]. The most common sites are the distal radius, distal tibia, fibula, and femur. Splinting is usually sufficient as buckle fractures are generally stable. However, they should be followed by an orthopedist. Casting may be done for 3 weeks to ensure healing if the child is likely to be noncompliant with the splint or if he/she is extremely active.

Plastic Deformation Fractures

A plastic deformation fracture occurs when the longitudinal forces overcome a bone's ability to recoil, leading to a bowing deformity. The most common locations are the ulna, radius, and fibula. Simple casting for 4–6 weeks is indicated if the deformation is less than 20° or the child is under 4 years old, as the angulation will self-correct. Reduction and/or surgical intervention may be needed if the deformation is greater than 20° or if the child is over 4 years old [4].

Greenstick Fractures

Greenstick fractures are fractures that do not extend completely through a bent bone, breaking one cortical surface without disrupting the other side. These fractures are considered unstable and have high rates of refracture [5]. The most common location of a greenstick fracture is the forearm. Orthopedics referral is needed, with regular follow-ups. Nondisplaced forearm fractures should be splinted until seen by an orthopedist for casting in a long arm cast for 3–4 weeks,

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followed by short arm casting for another 2–3 weeks [6].

Apophyseal Avulsion Fractures

Common apophyseal injuries, such as Osgood-Schlatter disease, Sinding-Larsen-Johansson syndrome, and Sever's disease, increase the risk of apophyseal avulsion fractures; repeated traction on the fibrocartilage can lead to a portion being pulled off the bone [7]. Most avulsion fractures, such as tibial tuberosity and inferior pole of the patella, result from an acute injury. These fractures need to be immobilized and often warrant an orthopedic referral to evaluate for the need for surgical intervention, to remove or reattach the avulsed bone, especially if there is displacement.

Stress Fractures

Stress fractures are most commonly seen in young athletic or active females but may also affect males. Mean age at the time of injury is around 14 years old. They are caused by overuse, which leads to microfractures. The majority of patients are able to attribute the onset of pain to a recent increase in activity level. On exam, there will be tenderness over the affected bone, with or without surrounding edema. However, if it is difficult to palpate the local area of bone due to overlying tissue, applying stress on the bone that is suspected to be involved may elicit pain, assisting with the diagnosis of a stress fracture. Plain radiographs maybe ordered. However, these usually remain normal until 2 weeks after the onset of pain. If there is a high clinical suspicion with negative radiographs, magnetic resonance imaging (MRI), a bone scan, or a single-photon emission computed tomography (SPECT) scan may be ordered, especially if time is a factor, as when a sports event is looming. Management will depend on the site of fracture. Conservative treatment with ice, acetaminophen, limited weight-bearing, and splinting is done for low-risk sites, whereas fractures in high-risk sites (Table 1) should be evaluated by an orthopedist [8]. Identifying modifiable risk factors (Table 2) when a stress fracture is suspected is extremely important for the management and prevention of another one.

Table 1 Stress fracture sites

Low-risk sites	High-risk sites
Second to fourth metatarsal shafts	Pars interarticularis of lumbar spine
Posteromedial tibial shaft	Femoral head
Proximal humerus	Superior side of femoral neck
Ribs	Patella
Sacrum	Anterior cortex of tibia
Pubic rami	Medial malleolus
	Tarsal navicular
	Proximal fourth and fifth metatarsal
	Great toe sesamoids

Table 2 Risk factors for stress fractures

Modifiable	Nonmodifiable
Low physical activity	Female
Increasing volume and intensity of physical activity	Irregular menses
Low BMI	Older age
Low dietary calcium intake	Prior stress fracture
Poor biomechanics	Family history of osteopenia or osteoporosis

Apophyseal Injuries (Apophysitis)

Apophysitis of the Hip

An apophyseal injury of the hip occurs in active adolescents, usually athletes in track, soccer, or gymnastics [9]. The injury can involve the anterior superior and anterior inferior iliac spines, iliac crest, or ischial tuberosity (Fig. 2). Typically, the patient will present with a dull pain in the hip that is associated with activity, with or without a history of trauma. On examination, there may be some localized tenderness. If ecchymosis is present, an avulsion fracture should be suspected. Radiographs of the hip and pelvis are not necessary; however, they are usually obtained to rule out other causes of hip pain. Treatment is based on severity of symptoms but must include avoidance of the aggravating activity, stretching the affected area, ice, and NSAIDs. If limping is predominant, limitations on weight bearing can be made. Children and adolescents should be enrolled in a rehabilitation program. Return to play should only be advised once full range of motion is achieved without pain, which may take anywhere from 4 to 6 weeks [9].

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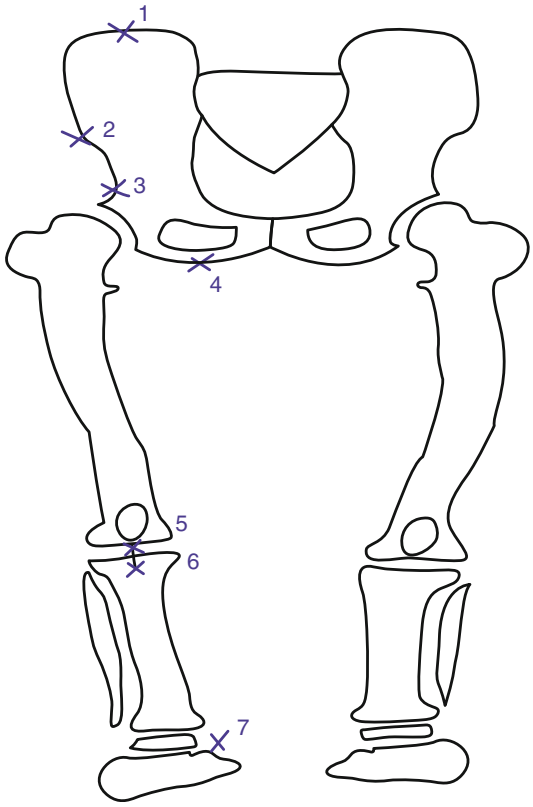


Fig. 2 Apophysitis locations. (*1*) Iliac crest; (*2*) anterior superior iliac spine; (*3*) anterior inferior iliac spine; (*4*) ischial tuberosity; (*5*) inferior pole of patella (Sinding-Larsen-Johansson); (*6*) tibial tuberosity (Osgood-Schlatter disease); (*7*) calcaneus (Sever's disease)

Sinding-Larsen-Johansson Syndrome

Sinding-Larsen-Johansson syndrome is an apophyseal injury, a type of osteochondrosis that occurs at the inferior pole of the patella (Fig. 2) after repeated microtrauma [10], usually in boys between the ages of 10 and 12 years old. They may complain of pain that is worse when walking up or down stairs or jumping. Usually, the only abnormal finding upon examination of the knee is tenderness and swelling at the inferior patellar pole. Fragmentation may be seen on anteroposterior (AP) and lateral plain radiographs. Treatment is geared toward pain control with NSAIDs, decreasing the inflammation with ice, and quadriceps rehabilitation. Resolution of symptoms may take 3–18 months [11].

Osgood-Schlatter Disease

Osgood-Schlatter disease is a common cause of gradual-onset anterior knee pain in children aged 9–13 years old. It is a traction apophysitis of the proximal tibial tubercle at the insertion of the patellar tendon. It can lead to limping, usually during growth spurts. Children often describe the pain as worsening with activities such as running, climbing, or jumping, but improving with rest. There is often tenderness to palpation over the tibial tubercle (Fig. 2) and reproduction of pain with resisted knee extension. Sometimes, a prominence may be palpated over the tibial tubercle. Radiographs, AP, and lateral views are usually not necessary but are done to exclude other conditions, especially if the pain worsens at night, which is not typical of Osgood-Schlatter's. The symptoms often resolve once the growth plate has closed. Until then, treatment includes ice, pain control with NSAIDs, and physical therapy [12]. If pain persists, referral to orthopedics may be considered for potential injection of 12.5% dextrose [13] or even surgical removal of the bony prominence. Referral to orthopedics is needed if the patient is unable to lift his/her heel off the table without bending the knee; this suggests an issue with the extensor mechanism, which may require surgery [14].

Sever's Disease

Sever's disease is considered an irritation of the calcaneal apophysis (Fig. 2), usually presenting in active adolescents (9–11 year olds), on average presenting earlier on girls (6 years old in girls vs. 8 years old in boys). These patients usually participate in sports which require a lot of running, and it may take 3–4 years to fully resolve [15].

Patients will often complain of unilateral or bilateral heel pain related to activity. Examination reveals tenderness of the calcaneal apophysis with weakened dorsiflexion, and gastrocnemius-soleus flexibility can be decreased. Imaging may be done to rule out other conditions, such as a unicameral bone cyst, if symptoms present unilaterally [14]. Management includes rehabilitation exercises and

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pain management with NSAIDs to help decrease the inflammation. The patient should be advised not to take any pain medication before activities so as not to mask the pain. Return to activities should only be done once pain subsides. Use of a ¼ in. heel lift with icing for 20 min per day can also provide relief [14]. Should symptoms persist after 4–8 weeks of treatment, casting for 3–4 weeks may be considered [9].

Osteochondritis Dissecans

Osteochondritis dissecans (OCD) occurs when subchondral bone and cartilage separate from the underlying bone. The most common locations of OCD are the knee and ankle, but it can also occur at the elbow, talus, and distal humerus. The patient will generally describe vague pain associated with swelling, clicking, and sometimes locking that gets worse with activity. On examination, there is tenderness over the lesion. When OCD occurs in the knee, the Wilson test may be positive, and there may be an antalgic gait [14]. The Wilson test is performed by having the patient lie supine and extend the knee from a 90° angle while internally rotating the tibia. It is considered positive when there is knee pain as the knee is extended with the tibia internally rotated; however, there is no pain when the same maneuver is performed with the tibia externally rotated. The medial femoral condyle will be tender to direct palpation when the knee is flexed to 90°. Plain radiographs should be obtained. If suspected in the knee, tunnel and lateral views should be included. MRI can be useful to visualize articular cartilage integrity. When the cartilage is intact, management can consist of modifying activity or placing the patient on crutches for 6–8 weeks [16]. Surgery might be needed to avoid early onset of degenerative joint disease if the child is already skeletally mature or if the articular cartilage has some damage. Orthopedic referral is indicated if the lesion is larger than 2 centimeters (cm) because such lesions can lead to complications, including early-onset degenerative joint disease [14].

Growing Pains

Growing pains are the most common cause of episodic musculoskeletal pain in children. These nonarticular leg pains occur at night in healthy active children 3–12 years of age, with a peak of 6 years. These leg pains are often felt in the calf but may also be felt in the foot, ankle, knee, or thigh. The pain episodes may last from minutes to hours. They are usually bilateral and are more common in boys and among children with laxity of the ligaments. The pain may be more likely to occur if the child has been particularly physically active during the day. The etiology is unknown, but it may be an overuse syndrome. There are no associated systemic symptoms such as weight loss, fevers, or fatigue [14]. The diagnosis is based on the clinical picture and a normal physical exam. If there are atypical symptoms, such as unilateral leg pain, further studies such as CT, MRI, x-rays, bone scan, or lab work should be obtained to rule out pathology. The differential diagnoses of growing pains include fractures, osteomyelitis, malignancy, metabolic systemic disease, and osteonecrosis; these should be excluded before a diagnosis of growing pains is made [14]. Treatment of growing pains consists of comforting the child, local massage, and analgesics. In a recent study, there was reduction of pain after vitamin D supplementation [17].

Regional Musculoskeletal Conditions

Neck and Back Problems

Spondylolysis and Spondylolisthesis

"Spondylolysis" is defined as the separation of the vertebral pars interarticularis, most commonly at L5, which may be unilateral or bilateral. About 25% of cases progress to spondylolisthesis, which is the bilateral defect that allows the vertebral body to slip anteriorly. There are several risk factors for spondylolysis, including occult spina bifida at S1, Scheuermann's kyphosis, and a family history of spondylolysis. These conditions are common among adolescent athletes with repetitive flexion and extension movements of the back,

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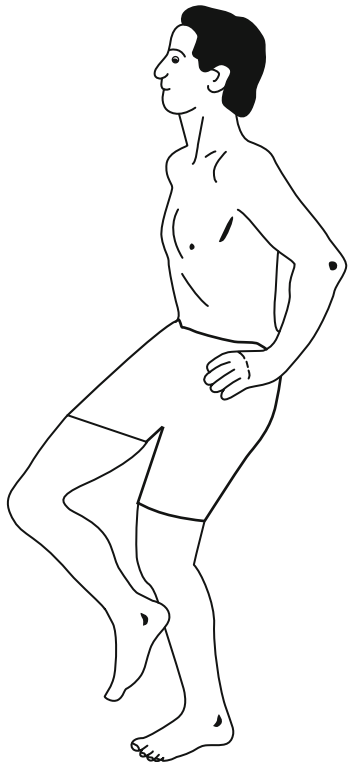


Fig. 3 The stork test: Ask the patient to lean backward while standing on one leg; considered positive if the back pain is reproduced on the same side the patient is standing on

causing an achy back pain that radiates into the buttock and posterior thighs. Symptoms improve with rest, but higher-grade slips can present with neurologic manifestations, such as urinary incontinence [14].

A positive Stork test suggests spondylolysis (Fig. 3). It is performed by asking the patient to hyperextend his/her back while standing on one leg; a positive test reproduces the back pain [18]. Palpation of the spinous processes can reveal a prominent process, suggesting significant spondylolisthesis. Observation of the gait may reveal high-grade spondylolisthesis in some patients, as they may walk with their hips and knees flexed (the Phalen-Dickson sign [19]). Plain radiographs with AP, weight-bearing lateral, and oblique views of the lumbosacral spine may help reveal the "Scotty dog" sign (Fig. 4), which is associated with spondylolysis [1]. If not well-visualized, additional imaging may be needed. If neurologic symptoms are present, obtaining an MRI is often helpful.

Symptomatic spondylolysis should be managed with activity restriction, possibly with thoracolumbosacral orthosis (TLSO) for pain management, and aggressive physical therapy. Treatment of spondylolisthesis will depend on the grading of slippage; however, early cases can

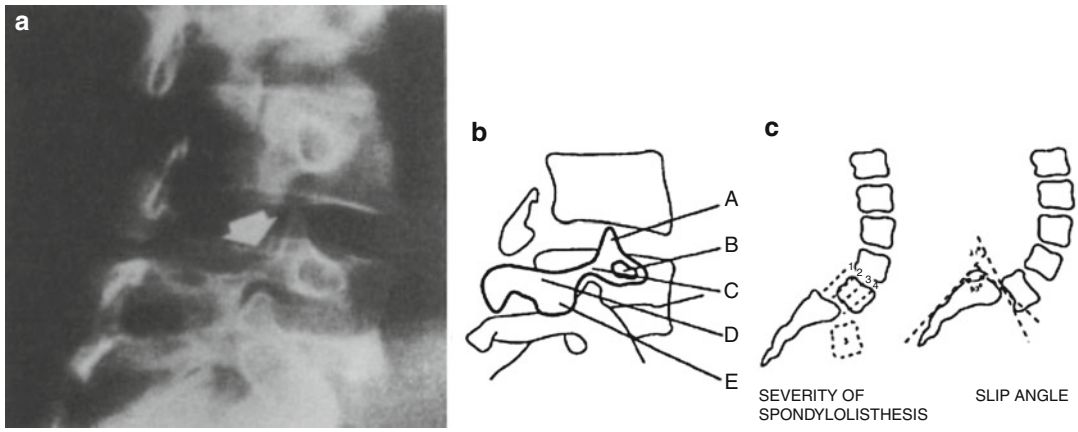


Fig. 4 Spondylolysis and spondylolisthesis (*right*). (**a**) Radiographic representation of an abnormal elongation (*greyhound sign*) of the pars interarticularis or the "neck" of a scotty dog (*arrow*). Other defects, such as sclerosis or lysis in the pars, are best visualized in this "neck." (**b**) "Scotty dog." *A* = superior articular process (ear); *B* = pedicle (eye); *C* = pars interarticularis (neck); *D* = lamina (body); *E* = inferior articular process (front leg). (**c**) Severity of spondylolisthesis and slip angle. (With kind permission from Springer Science+Business Media: Bracker and Achar [20])

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be managed like spondylolysis. Those with greater than 50% slippage and who are skeletally mature are candidates for spinal fusion. However, if there are neurologic signs, neural decompression may be needed in addition to spinal fusion [14]. Urgent additional imaging and intervention should be ordered if the following are present: <4 years old, fevers, weight loss, worsening pain, nocturnal pain, history of trauma, malignancy, or tuberculosis [21].

Idiopathic Scoliosis

Idiopathic scoliosis is defined as an abnormal lateral curve of the spine. This is further divided into subcategories based on the age of the child at diagnosis: infantile (0–3 years), juvenile (4–9 years), and adolescent (≥10 years). These children may present after a school screening, which is currently not supported by the US Preventive Services Task Force (USPSTF), or due to obvious asymmetry of the back, noted by others. It is important to establish when the asymmetry was first noticed, any associated symptoms, and signs of puberty. The Adam's forward bend test is commonly used to assess the rotational component of scoliosis, in combination with a scoliometer. The test is done by standing behind the patient, asking the patient to bend forward to reach for his/her toes, and then assessing for any asymmetry. When clinically suspected, scoliosis films (standing posteroanterior [PA] and lateral films of the entire spine) are needed to assess for the Cobb angle and skeletal maturity, via the Risser scale (Fig. 5) [23]. Lateral bending films are sometimes obtained for preoperative evaluation.

When there is low risk for progression in adolescent idiopathic scoliosis, the primary care physician can manage and follow with repeat scoliosis radiographs every 6–9 months. Orthopedic referral is indicated when there is any of the following [24]:

- More than 7° of trunk rotation
- A premenarcheal girl, or a boy between 12 and 14 years old, with a Cobb angle of 20–29°
- A Cobb angle of 30° or more in any patient
- Any patient with a progression of 5° or more of the Cobb angle

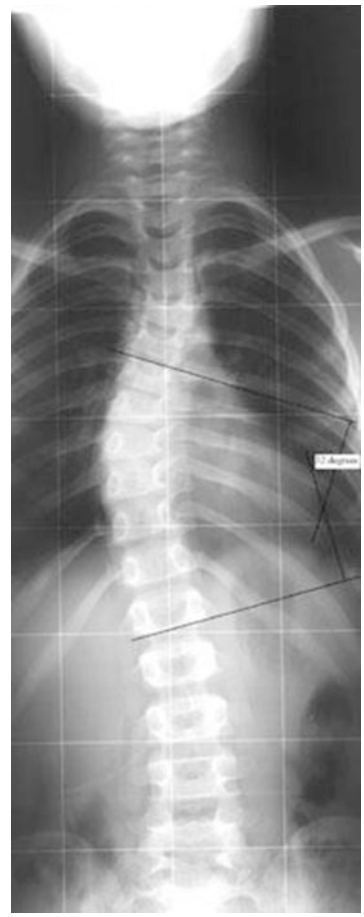


Fig. 5 Measurement of the scoliosis angle. Horizontal lines are drawn parallel to the end plates of the neutral vertebrae at the end of the curve. Where perpendicular lines intersect, the angle of scoliosis is measured. In this case, the angle of Cobb measures 32°. ([22]. With kind permission from Springer Science and Business Media)

Management of these patients will vary between bracing and surgical intervention. If surgery is performed, activity is usually restricted for several months after surgery.

Scheuermann Disease

Scheuermann disease or juvenile kyphosis is the anterior wedging of at least 5° in three adjacent thoracic vertebral bodies, usually found during early adolescence. It is associated with spondylolysis. It presents with subacute pain that worsens after activity and at the end of the day without a clear precipitating event. Upon

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examination of the child, a sharp angulation of the thoracic or thoracolumbar spine is observed, especially as the child bends forward. Some may call these patients "hunchbacked." Radiographs of the spine while standing, especially lateral views, are important for diagnosis. If the angulation is less than 60°, conservative management is usually tried, with hyperextension rehabilitation. However, for curves greater than 60°, bracing is often employed for as long as the vertebral end plates are not fused [25].

Elbow Problems

Osteochondrosis of the Elbow

Osteochondrosis of the elbow is also referred to as "Panner's disease." It is generally found in the dominant arm of young males between the ages of 7 and 12 years old and is the most common cause of lateral elbow pain in children less than 10 years old [26]. The full etiology is unknown, but it is most likely due to insufficient blood supply to the chondroepiphysis during a compressive force. This, in combination with active ossification of this age group, leads to local avascular necrosis and subsequent recalcification of the capitellum. They may complain of sudden onset lateral elbow pain that is reproducible on palpation. There may be decreased range of motion with extension. Plain radiographs, with AP and lateral views, may show an irregular joint surface with fragmentation of the capitellum. Panner's disease is managed by cessation of activities that place stress on the joint until imaging, and physical exam shows evidence of full healing, usually in about 6–12 weeks.

Radial Head Subluxation

Subluxation of the radial head is a common injury in preschool children aged 1–4 years old. It is commonly called a "pulled elbow" or "nursemaid's elbow" because it occurs from traction on the forearm while pronated and with the elbow extended. The child will have been observed not using the affected arm as usual. For an unknown reason, it is more common in the left arm [27]. On examination, the child is often observed holding the affected arm closely to the body, with the elbow extended. Tenderness is often present over the anterolateral aspect of the radial head. Plain radiographs with AP and lateral views are often obtained to exclude other causes or more serious bony injuries; still, the diagnosis can be made by history and physical exam alone. Management is reduction by either one of two methods: hyperpronation or supination with flexion [28].

In the hyperpronation method, the examiner supports the elbow and places steady pressure on the radial head while gripping the distal forearm with the opposite hand and hyperpronating the forearm. The supination with flexion method is also performed by supporting the arm at the elbow and applying pressure on the radial head, but the opposite hand maintains traction on the forearm; in one smooth motion, the elbow is fully supinated and flexed. The child will usually resume normal activity with the arm within 5–10 min after reduction. Patients whose elbows cannot be reduced initially should be examined for possible fracture. Reduction may be tried for up to two times; however, if the arm remains immovable, radiographic image is warranted [29]. Orthopedic referral is indicated after several failed attempts at reduction, at which point obtaining radiographs and placing the arm in a sling are recommended until evaluation by a specialist.

Gait Abnormalities

Normal Gait and Alignment

In order to recognize abnormal gait, it is important to be able to identify the natural progression of alignment and gait in children. From birth, the legs are slightly in varus (10–15°) and will gradually straighten to the neutral position at around 12–18 months of age. The legs then become valgus, with a peak of around 3–4 years old. By 11 years old, the valgus alignment improves to 5–7° [14]. Normal gait has two phases: stance and swing. These phases should be symmetrical when

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comparing the lower extremities, with the stance taking up 60% of the time of the entire gait [1].

Metatarsus Adductus

Intoeing is commonly secondary to metatarsus adductus, which is seen more in first children and is the most common cause of congenital foot deformity [30]. It is thought to be due to excessive uterine molding from the primigravid uterus. Although the children rarely have symptoms, parents tend to be concerned and may bring them in for a checkup. Examination may show an intoeing gait, often bilateral, and deep medial creases on the feet. Careful evaluation is extremely important since treatment is based on severity. To determine severity, the examiner should use the heel bisector method (Fig. 6), which entails drawing a line that divides the heel in half and continuing the line to see where it lands in relation to the toes [14]. Normally, the line will fall between the second and third toes. In mild cases, the line will fall in the middle of the third toe. In moderate cases, the line will be between the third and fourth toes. In severe cases, it will fall between the fourth and fifth toes. Imaging is usually not necessary but is done to exclude other causes in toddlers or older children who have persistent symptoms.

The majority of metatarsus adductus cases will self-resolve, but some may need treatment. Mild cases that can be passively corrected should be kept under observation. Stretching exercises should be performed by the parents at each diaper change for moderate cases that can be passively corrected by regularly moving the foot into a neutral position. The exercise entails applying laterally directed pressure on the first metatarsal head for 10 s. The parent should be instructed to perform it five times a day on each foot [31]. Severe cases that are rigid may be treated with serial casting for 6–8 weeks, with good outcomes, if started before 8 months old.

Tibial Torsion

Internal tibial torsion is a common cause of intoeing in toddlers and may be associated with metatarsus adductus and genu varum. The thigh-foot angle (TFA) should be estimated by measuring the angle between the longitudinal axis of the femur and the foot (Fig. 7). A TFA greater than 20° is excessive but will normally correct without any intervention at around 5 years of age [32]. Only when the torsion is severe (TFA more than 85°) should surgical intervention be considered.

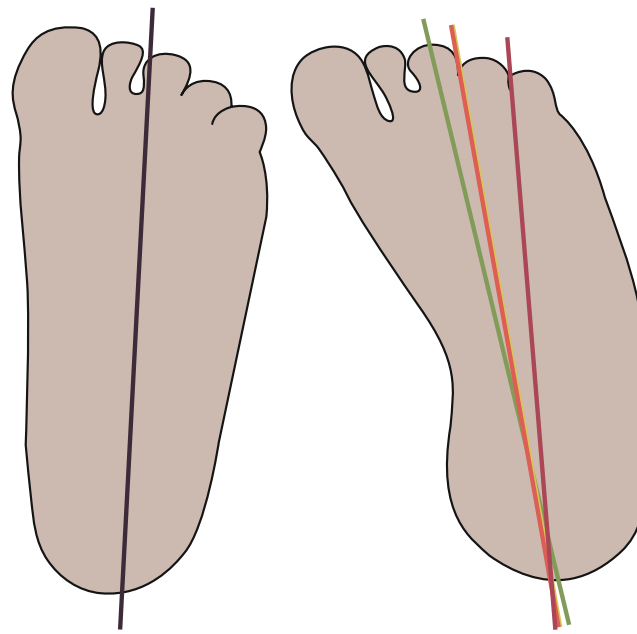


Fig. 6 Heel bisector method for determining metatarsus adductus severity. On the left, shows a normal heel bisector line drawn in black. On the right, a comparison of where the heel bisector line will fall in relation to the toes for mild (*green*), moderate (*orange*), and severe (*red*) metatarsus adductus

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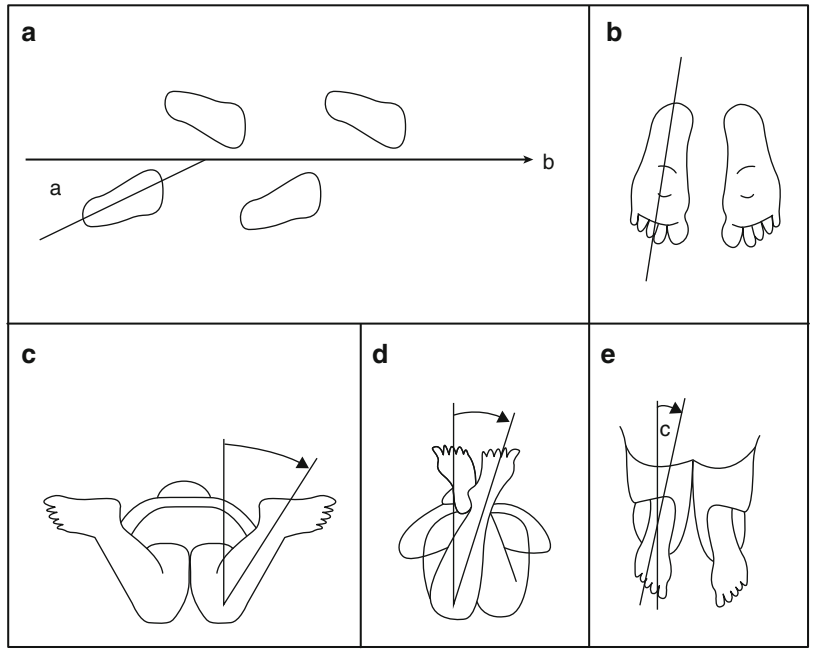


Fig. 7 Tests for torsional deformities. (**a**) Foot progression angle (*a*) is formed by the foot axis (**b**) and the line of progression (*b*). (**b**) Foot axis. (**c**) Measurement of internal femoral rotation. (**d**) Measurement of external femoral rotation. (**e**) Thigh-foot angle (*c*) is formed by the longitudinal axis of the femur and the foot axis. (From Bracker and Achar [20]. With kind permission from Springer Science and Business Media)

Femoral Anteversion

Children greater than 4 years old will commonly have intoeing secondary to femoral anteversion. Sitting in the classic "W" position [33] with their knees together and feet on either side can contribute to the femoral anteversion. While walking, the child's legs appear as if they were internally rotated; when running the legs will flip outward ("egg-beater" or "windmill" pattern). The hip will exhibit increased internal rotation with range of motion testing. Radiographs are usually unnecessary. Most cases require nothing more than observation, given that 85% will spontaneously resolve usually by 11 years of age [34].

Genu Varus

"Genu varus," also known as "bow-leggedness," is a common concern among parents because of the way it affects the appearance of the child's legs. Genu varus may cause children to walk with intoeing or have frequent falls. Depending upon the age of the child, genu varus could be completely benign, as all children are naturally born bowlegged. Genu varus may persist until the child is about 2 years of age. During this period, the recommended management is simply observation and reassurance. Pathologic causes include conditions such as Blount disease, nutritional rickets, trauma, metabolic bone disease, or even a neoplasm. Physical examination is useful in helping to distinguish pathologic versus physiologic etiologies. Asymmetric bowing with a lateral thrust upon walking is suggestive of a pathologic cause [35]. Radiographs of the entire lower extremity are known as teleograms and should be obtained while standing if suspecting a nonphysiologic cause. If a pathologic cause is found, it is recommended that the child be referred to an orthopedist or the specialist for the underlying etiology. The follow-up for an otherwise physiologic genu varus in a child should be every 4–6 months to ensure resolution.

Blount's Disease

Blount's disease is a pathologic cause of genu varus that is differentiated from physiologic bowing on physical exam and radiographs. Risk factors include African American lineage, early walking, and obesity. These children will present with an asymmetric angular alignment of the lower extremities and walk with a lateral thrust [35]. The teleograms will show the bowing deformity of the proximal tibia and medial beaking, with a downward slope of the proximal tibial

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metaphysis. There are two subtypes of Blount's disease: infantile and adolescent. The infantile type is usually diagnosed before the age of 4 years old and is bilateral, whereas the adolescent type can be unilateral or bilateral. The infantile type can be managed with braces to decrease the compressive forces and has a better prognosis if treatment begins before 3 years of age. If the varus deformity does not correct with bracing, then a referral to an orthopedist is warranted. In contrast, the adolescent form is more appropriately managed by an orthopedist because surgery with hemiepiphysiodesis or tibial osteotomy is the mainstay of treatment.

Genu Valgus

"Knock-kneedness," or "genu valgum," can also often present to a primary care clinician's office due to parental concern with the appearance of a child's legs and the clumsiness associated with this condition. Occasionally, the child may complain of pain in the knee or foot. Like genu varus, genu valgum is part of the normal progression of development, usually seen between the ages of 2 and 5 years old. When there are no other concerns of a potentially pathologic etiology such as trauma, a systemic condition, or a neoplasm, observation and reassurance is recommended. Worsening genu valgum after 4 years of age should raise suspicion regarding a pathologic cause. Clues found upon physical examination that make a pathologic cause more likely include [35]:

- Unilateral genu valgum
- Height that is below the third percentile
- Greater than 8 cm between the medial malleoli when the knees are extended, patellae pointed straight, and femoral condyles that are touching
- A medial thrust on ambulation

Similar to genu varus, when a pathologic cause is suspected, it is appropriate to obtain teleograms. The parents should be reassured if physiologic genu valgum is suspected, as it generally self-corrects when the patient is between 4 and 7 years of age. However, obese children should be followed regularly since they run a higher risk of developing worsening genu valgum [14]. Referral to orthopedics should be done for pathologic cases as they can lead to long-term consequences such as meniscal tears and higher rates of osteoarthritis.

Hip Problems

Developmental Dysplasia of the Hip

Formerly termed "congenital hip dysplasia," developmental dysplasia of the hip (DDH) refers to the abnormal development of the acetabulum and the proximal femur, which may occur as the child is developing and not always congenitally, hence the change in terminology. DDH may present at birth, with an abnormal gait as a toddler or activity-related hip pain in adolescents. Every newborn and child should be evaluated routinely for this condition until the child is walking normally.

The newborn hip exam should be performed on an infant who is not wearing clothes or diapers and should include the Barlow and Ortolani maneuvers. The Barlow maneuver is considered positive if there is a palpable clunk, while the hip is adducted with gentle posteriorly directed pressure, which signifies that the hip is dislocatable. The Ortolani maneuver should follow the Barlow maneuver and is considered positive if a palpable click is felt when abducting the hip while lifting the trochanter anteriorly, which assumes that the hip is reducible. Classically, Barlow and Ortolani maneuvers were performed together because when both are positive, diagnostic specificity increases to 99%; however, a recent reevaluation of examination techniques suggests that Ortolani's test is more important [36]. In children over 3 months of age, DDH is highly suspected if passive abduction of the hip is less than 45° [37]. Additional maneuvers include the Galeazzi and Klisic tests, which can help in detecting DDH in older children. The Galeazzi test is performed by having the patient assume the supine position with hips and knees flexed so that the feet are side by side and flat on a surface; the position of the knees are observed. The test is considered

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positive if the knee of the affected side is lower than the other. The Klisic test is performed by imagining a line between the anterior-superior iliac spine and greater trochanter to see where it falls in relationship to the umbilicus; if the line falls below the umbilicus, the test is considered positive. Children who have a positive Trendelenburg pelvic tilt test may also have DDH.

In the first 6 weeks of life, many newborns may have "clunks" due to normal physiologic laxity that may raise suspicion for DDH. Ultrasound screening for DDH is typically performed for infants younger than 4–6 months, however, should usually be postponed until at least 3–4 weeks of life to allow the normal laxity to resolve [38]. Older children and adolescents may be screened with plain radiographs. Confirmed cases should be referred to orthopedics. Treatment may involve utilizing a Pavlik harness and proceeding to surgery if it fails or if the patient is older than 18–24 months.

Transient Synovitis

Hip pain in a child aged 3–8 years old after a recent upper respiratory infection should raise suspicion for transient synovitis. Males are twice as likely to suffer from this condition than are females. Generally, the child will appear well but will have limited range of motion of the hip. If fever is present, it is often low grade. Basic laboratories including a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) should be obtained. The Kocher criteria [39] (refuses to bear weight on affected side, fever $\geq$101.3 F, ESR $\geq$40 mm/h, and WBC $>$12,000 cells/microL) are very useful in helping to guide the clinician. The likelihood of the presence of septic arthritis rises with each criterion met, and the presence of all four criteria makes the diagnosis of septic arthritis almost certain. Ultrasonography or MRI can be performed to identify if a joint effusion is present. If septic arthritis is not suspected, patients can be observed closely. If any signs or symptoms suggesting septic arthritis arise subsequently, then joint aspiration is recommended. Transient synovitis is managed conservatively with NSAIDs. Most patients make a full recovery within 1 week [40]. The child may return to activity as he or she tolerates it.

Septic Hip

As in adults, septic arthritis can be very damaging to the joint and therefore should not be missed. When septic arthritis occurs in the hip of a child, typically he or she will be ill-appearing and often febrile ($>$101 °F). The child may refuse to weight-bear or move the affected limb due to severe pain. Obtaining blood to check white blood cell count, ESR, and CRP is important. A high score using the Kocher criteria suggests septic arthritis [39] and typically the CRP is higher than 2 mg/dL. To confirm the diagnosis, an ultrasound-guided hip aspiration should be done with synovial fluid and blood cultures. Ideally, these should be done before starting antibiotics. Intravenous antibiotics should not be delayed, however, if the hip aspiration cannot be done in a timely fashion. Coverage should include the most common pathogens including *Staphylococcus aureus*, *H. influenzae* type B, and *Streptococcus pneumoniae*. Some patients may require repeated drainage of the hip joint so that blood flow is not compromised by the increased intraarticular pressure.

Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis (SCFE) must not be missed in children presenting with non-radiating, aching pain in the hip, groin, or upper thigh. There is usually no trauma associated with SCFE, but the pain worsens with activity and can cause patients to limp or even be unable to bear weight. SCFE is commonly found in obese, adolescent males ($>$95th percentile for weight). Examination will show a limited range of motion [14]. Often, the gait is altered. If the SCFE is unilateral, the patient may walk with a Trendelenburg gait; if involvement is bilateral, a waddling gait may be observed [41]. Plain radiographs of the hip with AP and lateral views should be obtained to confirm the diagnosis (Fig. 8). Upon diagnosis, immediate orthopedics referral is warranted because complications of SCFE include osteonecrosis of the femoral head and femoroacetabular impingement.

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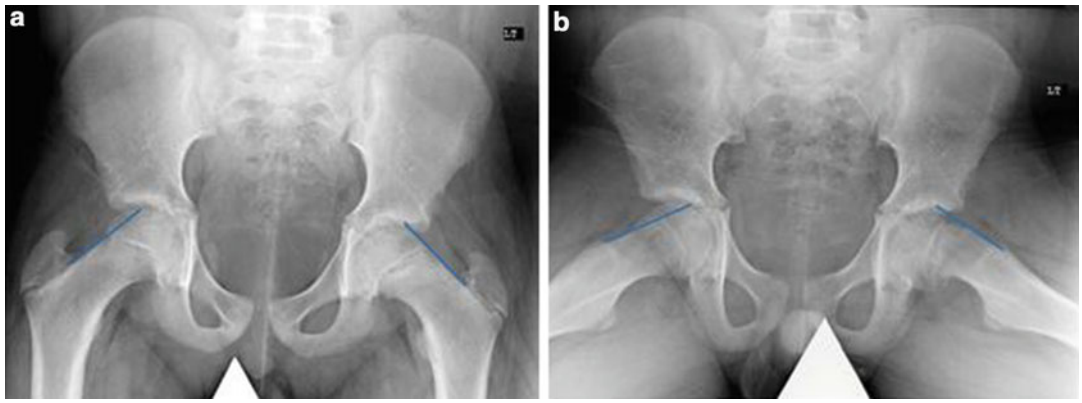


Fig. 8 Slipped capital femoral epiphysis. Image (**a**) is the anteroposterior (*AP*) view. Image (**b**) is the frog leg lateral view. The *blue line* on the AP (Klein's line) drawn along the femoral neck demonstrates the relative varus of the femoral epiphysis. A similar line drawn on the lateral demonstrates the relative posterior displacement of the left femoral epiphysis compared to the normal right hip. (From Lee [42]. With kind permission from Springer Science and Business Media)

Legg-Calve-Perthes Disease

Legg-Calve-Perthes disease (LCPD) is avascular necrosis of the proximal femoral head that typically presents in boys between the ages of 4 and 8 years old. Parents will often bring them in after the patients have been limping for about 3 weeks. The child may complain of groin pain radiating to the proximal thigh. Observation of gait may reveal an abductor lurch, while evaluation of range of motion will show a decrease in hip abduction and internal rotation. Although early LCPD may not show up on plain radiographs, they should still be done with AP and frog leg views. If radiographs are normal and clinical suspicion remains high, an MRI should be ordered. The frog leg views may show a crescent sign (Fig. 9), which is a late sign of LCPD.



Fig. 9 Perthes disease lucent crescent (*arrowhead*) of the outer femoral head on a frog-leg view in an 8-year-old boy. (From Oestreich and Crawford [43]. With kind permission from Springer Science and Business Media)

Although most cases are unilateral, LCPD can be bilateral. If found to be bilateral and symmetrical on imaging, additional workup is required with imaging of the hands, knees, and spine to rule out epiphyseal dysplasia [14]. Children should be made non-weight bearing, and orthopedic referral should be made for any child older than 6 years, or children younger than six, who have significant involvement of the femoral head. Early stages of LCPD can be managed with activity restriction, pain control, and close follow-up to monitor range of motion. Physical therapy may be prescribed to maintain range of motion. Containment treatment can be done for those with poor prognosis (i.e., children greater than 6 years of age at onset) [44]. Containment treatment involves various methods of keeping the femoral head within the socket to allow remodeling of the femoral head as it heals.

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Foot Problems

Toe Walking

Toe walking can be a parental concern, although the children are usually asymptomatic. In idiopathic cases, the child will start walking on time but will walk on his/her toes. This condition usually resolves itself in 3–6 months. However, if upon examination passive dorsiflexion is less than 10°, an Achilles tendon contracture might be present. An Achilles tendon contracture is treated with serial short leg casting over 6 weeks, with each cast increasing the amount of dorsiflexion of the foot and ankle. Rehabilitation is also appropriate for those with mild contractures. Imaging is usually only performed if the history is unclear or if there is a question raised upon examination. An orthopedic surgery referral should be initiated if there is suspicion of a fixed heel cord (Achilles contracture) or if toe walking is unilateral, as this almost always has a pathological etiology [14].

Talipes Calcaneovalgus

Positional calcaneovalgus feet or talipes calcaneovalgus is very common among newborns, secondary to the uterine positioning [1]. After birth, the foot appears hyperdorsiflexed and abducted, appearing as though it is flipped and resting on the lower anterior leg. Imaging is not necessary unless the case is questionable, in which case obtaining simulated weight-bearing radiographs is appropriate. The majority of cases will self-resolve, but casting may be necessary if the foot and ankle cannot be plantar flexed past the neutral position.

Talipes Equinovarus

Talipes equinovarus, also known as "clubfoot," occurs when one or both feet appear overly plantarflexed and inverted. It can be caused by many etiologies and can be categorized into congenital, syndromic, and positional. Parents usually raise concerns due to the appearance of the foot; however, early on, children are asymptomatic. If left untreated, talipes equinovarus can lead to difficulty wearing normal shoes, pain, and a gait disturbance. Physical examination may demonstrate high arches, forefoot adduction, heel varus, and ankle equinus. It is important to assess the rigidity of the foot. Imaging with weight-bearing AP and lateral views is obtained in older children but not necessary in infants. Children with talipes equinovarus are usually managed by orthopedists with the Ponseti method, which entails long leg casting and subsequent bracing [45].

Pes Cavus

"Pes cavus" refers to abnormally high-arched feet which can be due to neurologic disease, residual clubfoot deformity, or idiopathic causes. Children with pes cavus will have difficulty wearing shoes and complain of pain in the forefoot. Examination should include an evaluation of the alignment of the ankle, heel, midfoot, and toes. In many cases, there will be calluses under the metatarsal heads. When pes cavus is suspected, AP and lateral films should be obtained to evaluate the alignment by passing a line from the axis of the talus to the first metatarsal, which will show an increased angle. All children with pes cavus should be referred to orthopedists; however, while awaiting their visit, arch supports and shoe modifications may be helpful [14]. Rehabilitation can also be prescribed to strengthen the foot muscles and to promote range of motion. When these measures fail, surgery may be a consideration.

Flexible Versus Rigid Flatfoot

Parents are often concerned if their child's foot is flat also known as pes planus. There are different types of flatfoot, and it is important to determine if the condition is flexible or rigid flatfoot, because the management can vary. Flexible flatfoot is rarely symptomatic; if it is, the patient will usually complain of an inability to keep up with his or her peers or feel discomfort in the medial hindfoot related to activity. Performing the Jack test is a quick and easy way to make the differentiation: the child is asked to stand on his/her toes and the clinician observes whether the foot's arch is restored [14]. If it is, then it is considered flexible; if it is not, then it is rigid. In children who have symptoms, it is appropriate to obtain plain

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Table 3 Orthotics for pes planus (flatfoot) [46, 47]

Stating orthotic type	Type of support given
Internal heel wedges	Applied medially provide hindfoot inversion
University of California Biomechanics Laboratory (UCBL) orthosis	Provides longitudinal arch support by encompassing heel and hindfoot
Heel cup	Provides calcaneal support

radiographs (AP, lateral, and oblique views) to rule out other causes.

Management of flexible flatfoot can be done by the primary care clinician as most cases improve on their own; therefore, reassurance is key. However, if symptoms persist, shoe inserts can be prescribed to give arch support (Table 3). Rigid flatfoot usually requires some intervention, whether it be orthoses, serial casting, or even surgery. Management of rigid flatfoot should be geared toward its cause and may even require orthopedic referral.

Tarsal Coalition

Tarsal coalition is one cause of rigid flatfoot. It is due to abnormal connections between two tarsal bones. Symptoms usually start late in childhood and can be related to a change in activity. Parents may observe that the child is walking with a limp. Upon examination, rigid flatfoot is found with restricted hindfoot motion. Radiographs including AP, lateral, and oblique views are first-line imaging and should be obtained to confirm the coalitions. If they are not well visualized, a computed tomography (CT) scan is the gold standard and may be ordered to confirm the diagnosis. Management depends upon the severity of symptoms. If there are minimal symptoms, observation is appropriate; mild to moderate symptoms may require a short leg walking cast for 4–6 weeks [14]. Cases that are persistent after nonsurgical treatment may require surgical intervention to remove the coalition.

Freiberg Disease

Osteonecrosis of the metatarsal head is called Freiberg disease, which typically presents in adolescent girls. It is due to ischemia that most commonly affects the second metatarsal head but may also affect the third or the fourth metatarsal head [48]. The patient may describe a feeling a dull, aching pain in the forefoot that is worsened with activity and can be related to a trauma. There will be tenderness and edema of the metatarsal head with pain on dorsiflexion. Although plain radiographs can show fragmentation of the metatarsal head with flattening, this usually does not appear until 2–3 weeks after the onset of symptoms. Management depends on the severity of symptoms. For mild symptoms, rest and modification of activities may be sufficient. However, if the pain becomes particularly bothersome, short-term casting to allow for non-weight bearing on the affected metatarsals may be needed. In persistent cases, surgery may be done to remove loose bodies or realign the bone [14].

Kohler Disease

Similar to Freiberg disease, Kohler disease is osteonecrosis, but of the navicular bone. In most cases, it is unilateral and presents more commonly in males between the ages of 4 and 8 years old. Patients may present with foot pain and limping. On examination, there is tenderness and swelling at the medial arch. Observing the child's gait may reveal a limp, with the affected foot turned out more than the other while walking. Plain radiographs show a smaller navicular. Patients tend to do well without treatment, as the condition can spontaneously resolve. Those with more pain can be treated with a short-term walking cast for 4–8 weeks [49].

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Selected Problems of Infancy and Childhood

20

Laeth S. Nasir and Arwa Nasir

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Developmental Surveillance

The first year of life is marked by the highest rate of growth and development. The brain doubles in size in the first year of life and increases in size by another 15% in the second year. Developmental skills are acquired at a very high rate in infancy so that even minor disruptions in development at this stage can have serious long-term implications [1]. The goal of developmental surveillance in infancy is early identification of any deviations or disruptions to the normal growth and developmental trajectories. Identification should then lead to developmental and medical evaluation. Early intervention in children has been shown to improve functional outcomes for children with developmental delays [2].

The American Academy of Pediatrics recommends that developmental surveillance be incorporated into every well-child visit through the fifth year of life [3]. Developmental surveillance includes identifying risk factors for developmental delay, eliciting parental concerns, the clinical assessment of developmental milestones, and the administration of screening instruments.

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Common risk factors for developmental delay include genetic diseases, congenital malformations, and prenatal factors such as congenital infections and exposure to drugs. Environmental factors include maternal depression, nutritional deficiencies, and toxic stress. A family history of genetic syndromes or developmental delay is important in assessing the risk for developmental delays (Table 1).

Eliciting parental concerns is important, because the parent has intimate knowledge of the child and has the opportunity to observe him or her over time. Additionally, research indicates that parental assessment or concerns about their child's development are generally accurate [4, 5]. Additionally, asking the parents for their concerns strengthens the therapeutic alliance with the parents and engages them in monitoring the development of the child.

The classification of "streams of development" remains helpful as a framework for understanding and evaluating development in infancy and early childhood. The streams of development include the domains of gross motor, fine motor, social, and language development. A fifth dimension of intellectual and cognitive development is sometimes added to assess global function and intelligence.

Neurodevelopment generally follows a predictable course. For example, motor development tends to progress in a cephalocaudal and proximal to distal fashion. However, individual variations are common.

Clinical assessment of development involves eliciting the acquisition of milestones in each stream of development at the appropriate age.

Motor milestones are generally easily observable during the visit such as neck control, sitting, standing, or walking [6]. Fine motor milestones such as object manipulation can also be observed during the exam. Verbal and social skills may be more difficult to elicit from the child during the brief visit in the unfamiliar environment of the doctor's office, and the clinician may have to rely on parental report for those milestones (Table 2). A complete assessment of development should also include an assessment of growth as well as a general physical and neurological assessment to detect any associated abnormality or risk factors.

The use of developmental screening instruments improves the accuracy of detection of developmental delays significantly, and their use is recommended periodically [7]. Several validated developmental screening instruments are available. The American Academy of

Table 1 Risk factors for developmental delay

Genetic and chromosomal abnormalities	Chromosomal defects: Down syndrome, fragile X syndrome, Klinefelter's syndrome, Noonan syndrome, Williams syndrome, Angelman syndrome, Rett syndrome, Prader-Willi syndrome
	Inborn errors of metabolism, mitochondrial diseases, lipid storage diseases, etc.
	Muscular dystrophy syndromes
Congenital malformations	Lissencephaly, holoprosencephaly, thyroid agenesis, etc.
Intrauterine	Drugs and toxins: Alcohol, illicit drugs, teratogens
Exposures	Congenital infections: (TORCH)
	Malnutrition (IUGR), placental insufficiency
Perinatal and postnatal	Prematurity
Conditions	Birth asphyxia or birth trauma
	Neonatal infections especially CNS infections
	Emotional deprivation
	Experiential deprivation
	Sensory deprivations: Hearing or visual impairment
	Malnutrition, iron deficiency
	Exposure to toxins: Lead poisoning
	Severe congenital heart disease requiring surgery

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Table 2 Normal developmental milestones

Age	Gross motor	Fine motor	Social emotional	Language
2 weeks		Coordinated and effective sucking	Soothed by maternal voice	Startles to voice
		Hands fisted near face		
2 months	Lifts head off bed in supine position	Hands fisted	Social smile	Coos in response to social
4 months	Lifts chest off the table	Unfisted	Laughs aloud with	Vocalizes when alone
	No head lag when pulled to sit			
6 months	Tripod sit	Transfers object from hand to hand	Babbles, gestures for up	Babbles interactively
	Leads with head when pulled to sit			
	Rolls over in both directions			
9 months	Crawls on hands and knees	Inferior pincer grasp	Searches for family: Where is mama?	Mama, dada, nonspecific
12 months	Walks awkwardly	Mature pincer grasp	Proto-imperative pointing (points to a subjects he/she wants)	Mama, dada plus 3 words
15 months	Walks well		Proto-declarative pointing: (points to share experiences with parent)	Uses 3–5 words, names 1 object
	Recovers to standing from stooping			Mature jargoning
18 months	Runs awkwardly	Feeds self with a spoon	Points to 3 body parts	Uses 10–25 words
	Throws a ball walks upstairs with hands held			Names one picture on demand
24 months	Runs well	Follows a 2-step command	Parallel play	50 words or more, 2-word sentences, 50% intelligibility, knows own name
	Kicks a ball			
	Throws a ball overhand			
30 months	Jumps in place	Imitates horizontal line	Imitates adult activities	Knows pronouns (refers to self as I) and prepositions (up, in, out)
	Kicks ball throws ball overhand	Takes clothes off		
36 months	Rides a 3 wheeler	Copies circle	Starts sharing	200+ words, 75% intelligibility, 3-word sentences uses plurals names body parts
	Catches ball	Feeds self with a spoon	Knows name and gender	

Pediatrics recommends the administration of a standardized developmental screening instrument at 9, 18, and 30 months and the administration of an autism screening tool at 18 and 24 months. The USTSPF recently stated that there is insufficient evidence to support recommendations for or against screening for autism or speech and language disorders [6].

It is important to realize that some variability exists between children due to child or environment-related variables. However, significant delays should raise suspicion especially in the presence of risk factors and should prompt an evaluation or close monitoring. Table 3 provides a list of red flags that should raise alarm and prompt a workup.

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Table 3 Developmental red flags

Rolling over before 3 months	Indicates increased tone
Not walking by 18 months	Muscle weakness
No words by 18 months	Speech delay: hearing impairment, cognitive delay, ASD, etc.
Hand laterality before 12–18 months	Weakness of the other side
Not sitting by 7 months	Muscle weakness
Isolated fine motor delay	Visual impairment

If developmental delay is suspected based on the above evaluation, further assessment will be necessary to determine the cause. However, this evaluation should not delay the referral for rehabilitative services such as speech therapy, which are often helpful regardless of the cause of the delay.

In the USA, under the Individuals with Disabilities Education Act (IDEA), children from birth to 3 years can receive services with a general diagnosis of developmental delay. The management of children with developmental delays often requires a multidisciplinary approach. Children with severe developmental delays are prone to a host of complicating conditions such as seizure disorders, feeding difficulties, respiratory complications, and musculoskeletal complications. Care coordination is extremely important in the optimal management of these children.

Support is also needed for families who care for children with developmental delays to help manage the added physical and emotional burden and manage the needs of other typically developing children in the family.

Approach to the Infant or Child with Motor Delay

The approach to the evaluation of a child with motor delay depends on whether there are associated delays in one or more of the other streams of development. Global developmental delay (GDD) is diagnosed when delay is present in two or more streams of development.

Pure motor delay, in which the child has significant delay in achieving the motor milestones, can result from defects in the central nervous system, the neuromuscular junction, or in the muscles.

The evaluation of children with motor delay starts with the history, where special attention should be paid to perinatal history including pregnancy exposures and complications, delivery complications, prematurity, and postnatal course including neonatal illness and NICU admissions. Family history of neuromuscular disease or deaths in the neonatal period or infancy should be sought.

Prematurity is a common risk factor for developmental delays, with 11–12% of babies in the US born prematurely [8]. Therefore, premature babies require close developmental surveillance.

A complete and thorough physical examination with special attention to dysmorphic features, growth parameters, hepatosplenomegaly, and head circumference should be done. A full neurological evaluation including special attention to muscle tone and reflexes is critical for the diagnosis. Motor delay associated with dysmorphic features, growth delay, or delay in other milestones should raise the suspicion of a genetic syndrome, chromosomal defect, or a metabolic disorder. Increased muscle tone usually points to a CNS abnormality and is the hallmark of cerebral palsy. When a CNS cause is suspected, and a clear history leading to the diagnosis of cerebral palsy is not available, neuroimaging should be considered.

Severe hypotonia present at birth should raise the suspicion of congenital neuromuscular diseases such as Werdnig-Hoffmann Syndrome. Later-onset progressive hypotonia is a hallmark of muscular dystrophy.

It is important to remember that delays in achieving motor milestones can sometimes be caused by medical problems. Examples might include a delay in walking caused

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by developmental dysplasia of the hip, nutritional deficiencies such as rickets, or hypothyroidism [9].

Decreased muscle tone in the presence of motor delay points either to a systemic condition or to a defect in the muscles or neuromuscular junction. Metabolic conditions such as hypothyroidism as well as a number of the inborn errors of metabolism are associated with hypotonia and motor delay; however, most of these metabolic conditions are associated with delays in the other streams of development as well as other organ system dysfunction which may manifest as hepatitis, hepatomegaly, or seizures. Inherited diseases of the neuromuscular junction such as Werdnig-Hoffman disease causes severe hypotonia and motor delays and is usually fatal without invasive respiratory support. Muscular dystrophies have a later age of onset depending on the specific syndrome and are associated with progressive deterioration of muscle function. These disorders are distinguished from CNS and neuromuscular disorders by the presence of a high creatine kinase (CK) levels in the blood [10].

Red flags in the evaluation of motor delay that are indications for urgent referral to a pediatric neurologist include high CK levels indicating muscular dystrophy and the presence of muscular fasciculation indicating spinal muscular dystrophy. Loss of motor milestones is always abnormal and generally indicates a degenerative brain disorder. Patients in these categories are at risk of rapid deterioration of muscle tone that may threaten their vital functions such as swallowing and respiration.

Management of children with motor delay depends on the diagnosis. Children with motor delay regardless of the cause, however, usually will benefit from physical and occupational therapy, which aims to maximize function and prevent secondary developmental losses as a result of the original insult. Mobility and physical competence are essential for the exploratory behavior necessary for the development of other motor, social, and cognitive skills. Studies have documented that improved physical capacity results in significant improvements in language and problem-solving skills [11].

Speech Development and Speech Delay

Language development starting in the second half of the first year is largely dependent on the volume and quality of auditory input and the quality of the social environment. A positive social response to an infant's vocalizations is critical for the continuation of attempts to talk. Additionally, intact motor skills are necessary for the production of speech in infants.

Cognitive delay regardless of the cause is associated with speech delay. Cognitive delay can be one of the manifestations of a chromosomal aberration such as Down syndrome. Newer chromosomal and genetic testing is identifying chromosomal abnormalities associated with cognitive delays such as the 22q11.2 deletion syndrome [12].

However, in many situations the cause of the delay is never identified.

Speech delay is also a common presenting feature of autism spectrum disorder (ASD) and may or may not be associated with cognitive delay.

It is estimated that 40% of children with ASD have cognitive delays; however, even among those with normal cognition, speech and language development of children with ASD is often atypical.

Whether or not another diagnosis is present, early speech delay is associated with later language and reading disorders and the development of behavioral problems in late childhood and adolescence [13].

Evaluation of speech delay starts with a general evaluation to rule out risk factors including the presence of congenital or genetic syndromes. Family history of cognitive delay, ASD, or speech delay must also be sought. Physical examination including a thorough neurologic and assessment of the other streams of development may help to identify conditions that may increase the risk for speech delay. Early hearing evaluation should always be pursued in a child with speech delay. In addition, an assessment of the social environment including the nature of caregiver interactions with the infant is another critical part of the evaluation of speech delay.

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In children where speech delay is associated with communication and social interaction deficits, ASD should be considered and placed high on the differential diagnosis.

As with other forms of developmental delay, intervention in the form of speech therapy should not be delayed pending the establishment of the diagnosis. Children who have ASD and other associated deficits may benefit from special behavioral therapy. The diagnosis and management of ASD is discussed in ▶ Chap. 37, "Developmental Disability Across the Lifespan."

Recent research on language development indicates that language development in children can be enhanced by a rich and interactive linguistic environment beginning at birth. This includes responsive verbal interaction and reading to children. Promotion of early literacy by encouraging parents to interact verbally with their children and to read to their children regularly starting in the first year of life has been shown to be an effective strategy to improve language development. Additionally, there are convincing data that exposure to screen media in early childhood can result in delays in language and social development [14]. The American Academy of Pediatrics recommends that primary care physicians counsel parents to completely eliminate exposure to screen media in the first 2 years of life and to limit exposure to less than 2 hours thereafter.

Cognitive Impairment

Cognitive impairment is classified as mild, moderate, severe, and profound. The causes of cognitive impairment include genetic, metabolic, prenatal exposure to toxins or infections, and postnatal CNS insults. The more severe types of cognitive delay are more likely to have an identifiable etiology, whereas mild delays are more commonly idiopathic. In most children with moderate to severe cognitive impairment, other developmental delays are evident, allowing detection in infancy and early childhood. On the other hand, it is not uncommon for a child with borderline or mild intellectual disability to escape detection until after they enter school.

Children with mild to moderate cognitive delay often present with school underperformance. In addition to a thorough history and physical examination as outlined above, the workup of a child with isolated cognitive impairment should include genetic testing [15].

Evaluation of children with mild to moderate cognitive delay not associated with other diagnoses usually requires psychometric testing, which can be done through the school system.

Cognitive impairment is also associated with increased risk for behavior problems, including difficult to manage temper tantrums and disruptive behavior.

In the USA, children with cognitive delay qualify for special education services through the IDEA act. Referral for early childhood intervention services should be made early in the course of diagnosis, while further evaluation proceeds.

Oral Health

Dental caries has been called a "hidden epidemic." The Family Physician is often the first point of care for infants and children and their families and can be important in helping to provide oral preventive care and counseling during the most critical period for the development of dental disease. Disparities in the incidence of dental caries and access to dental care are more pronounced in the USA than those for general health. Six groups of children who are at high risk for dental caries have been identified [16]:

1. Children with special healthcare needs
2. Children of mothers with a high incidence of caries
3. Children with demonstrable caries, plaque, demineralization, or staining
4. Children who sleep with a bottle or are breastfed through the night
5. Later order offspring
6. Children in families of low-socioeconomic status

The American Academy of Pediatrics recommends that primary care providers be trained in

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Table 4 Anticipatory guidance for prevention of dental caries

Preventive strategies	Counseling points
Dietary counseling	Exclusive breast feeding for 6 months
	Continue breast feeding until 1 year or more
	Discourage bottle in bed
	Wean bottle by 1 year
	Avoid sugary drinks
	Limit 100% juice to 4–6 oz./day
	Only water between meals
	Model healthy eating habits
Oral hygiene	Model oral hygiene and consistent brushing
	Brushing twice daily with a smear of fluoride toothpaste
	Supervise brushing until age 8
Fluoride	Drink fluoridated tap water
	Use fluoride toothpaste
	Apply fluoride varnish 2–4 times per year starting with the eruption of the first tooth
Establish a dental home	Refer to a dentist by the first birthday
Dental injury prevention	Cover furniture corners
	Proper use of car safety seats
	Awareness of electrical cord risk for mouth injuries
	Use mouth guards in contact sports

performing oral health assessments on all children beginning at 6 months of age to identify known risk factors for early childhood dental caries and also to provide anticipatory guidance and dental referral by 1 year of age (Table 4).

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Group A Streptococcal Infections (PANDAS)

The first neuropsychiatric syndrome linked to group A streptococcal (GAS) infection was Sydenham's chorea, associated with rheumatic fever [17]. More recently, other neuropsychiatric manifestations have been described in association with GAS [18].

Table 5 Criteria for diagnosing PANDAS

1. Presence of a tic disorder or OCD.
2. Prepubertal age of onset [3–12].
3. Temporal association between symptom exacerbation and streptococcal infection.
4. Abrupt onset of symptoms and episodic course of symptom severity.
5. Presence of neurologic abnormalities during periods of symptom exacerbation.

PANDAS describe a subgroup of children who present with acute-onset obsessive-compulsive disorder (OCD) or tic disorders that follows an episode of Group A streptococcal infection. Additionally, children may have an acute episodic exacerbation of a preexisting OCD or tic disorder following GAS infections. In many situations, the neuropsychiatric symptoms resolve promptly after the successful treatment of GAS infection. The association is proposed to be immune mediated, although an etiologic association between GAS infection and neuropsychiatric symptoms has not been proven. Proposed criteria for diagnosis [19] are listed in Table 5.

This phenomenon is strictly limited to the pediatric age group, which is necessary to make the diagnosis. Some authorities recommend testing for GAS in any child presenting with acute neuropsychiatric symptoms such as tics or OCD, or with episodic exacerbations of existing OCD or tic symptoms. Appropriate treatment of GAS is discussed elsewhere. Treatment with immune modulating drugs is not recommended outside of research settings. Symptoms of OCD and tic disorder should follow standard treatment guidelines. The response to therapy is similar in patients with and without associated GAS infection.

Although antibiotic prophylaxis is effective and recommended for the prevention of Sydenham's chorea, it is not recommended in the prevention of PANDAS pending studies that explore the pathophysiology of its relationship with GAS and studies of treatment outcomes.

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Lead Poisoning

Lead is a heavy metal that does not occur naturally in the body and has no physiological role. Lead is toxic to all living cells, and the accumulation of lead can lead to dysfunction in almost all organ systems in the body. Children have an increased risk of lead poisoning because of their mouthing behavior and increased rates of lead absorption, especially when iron deficiency coexists, which is common in early childhood. Children are also particularly vulnerable to leads' toxic effects. Most importantly, the developing brain is highly susceptible to the toxic effect of lead. Quite low levels of lead exposure have been found to cause permanent and irreversible learning and behavioral problems.

Although lead poisoning has decreased in the USA since the 1970s following the elimination of lead from gasoline, paint, and the canning of food, certain pediatric population groups remain at high risk for lead poisoning. For those children, the CDC recommends routine screening at 12 and 24 months and at any time until 5 years of age if they have not been tested before [20]. These high-risk groups include:

1. All children who live in areas with 27% of housing built before 1950.
2. Populations in which the percentage of 1- and 2-year-olds with elevated blood lead levels is 12% or greater.
3. Children who receive services from public assistance programs for the poor such as Medicaid or the supplemental food program for women, infants, and children (WIC).
4. Children who screen positive by parental questionnaire.

Blood lead levels above 5 mcg/dl should initially be confirmed with a venous sample. If confirmed, it should prompt a home visit by the health department to inspect the home, day care, or any other place that the child spends time. The discovery of any source of lead should lead to proper treatment and abatement of the source, followed by re-evaluations of the blood level of the child to ensure that the levels decline. Other children living in the same household should also be tested.

Blood lead levels above 45 mcg/dl should be treated with chelation [21]. There are several compounds used to treat lead poisoning and different regimen recommendations depending on the severity of the intoxication. Because of the side effect profile of chelation drugs and the lack of experience among many clinicians in the use of these agents, the services of a toxicologist with expertise in chelation is helpful in the management of these patients [22].

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Health Care of the Adolescent

21

W. Suzanne Eidson-Ton

The care of adolescent patients is similar to care for any other patient in many ways. However, adolescence is a period of rapid change as teenagers' transition from childhood to adulthood, with all of the concomitant physical, intellectual, psychological, and sexual changes. It can be quite a chaotic time for both teens and their families. For family physicians, the primary role is often to help smooth this transition by helping families and their teenagers understand all of the changes happening, supporting teens in safe and healthy risk taking, and encouraging the gradual differentiation that is occurring.

Ideally, all visits with teenagers will include time with the family together, time with the adolescent alone, and time with the parent/guardian(s) alone. Especially in new patient adolescent visits, it is very important to establish the extent of confidentiality to which teenagers have a right, and the limits of that confidentiality. It is also important for teens to understand what services they may consent to and receive without their parent/guardian(s)' knowledge or consent. This will vary from state to state, but will usually include some reproductive health services and perhaps limited mental health and drug/alcohol services. It is important to know local laws regarding consent of minors, so that one can appropriately counsel and treat adolescent patients and their families. An overview of minor consent laws by state in the USA can be found at: https://www.guttmacher.org/state-policy/explore/overview-minors-consent-law.

Regarding confidentiality, it is best practice to start a new patient visit with both the teen and her/his parent/guardian(s). It is important to begin the visit by letting the family know that they will be seen all together first in order to discuss everyone's concerns. It is also recommended to let them know early in the visit that the teen will then be seen alone, explaining that he/she has a legal right to confidentiality about anything s/he discloses unless they tell the physician that s/he plans to hurt him/herself, someone else, or that someone is hurting them. (Please note that the author is using a variety of pronouns to be as inclusive as possible.) As mandated reporters, family physicians must report suspected child abuse to the appropriate authorities (Child Protective Services – CPS) and must treat suicidal or homicidal intent as would be done with any other patient. Otherwise, whatever the teen discloses to the physician must be kept in confidence. This does not mean, however, that secrets should be encouraged between teens and their parent/guardian(s). In fact, in many situations, it is helpful to encourage teens to talk with their parent/guardian(s) about the things they have shared, and the physician can offer to be present during the discussion, if the teen thinks that would be helpful.

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Some early adolescents may be quite intimidated to meet with a provider alone, but this is an important pattern and precedent to set, so that they and their parent/guardian(s) understand that this will happen at every visit. For very emotionally immature adolescents, the physician may meet with them very briefly, only to determine if there is anything else that requires discussion and to screen for abuse. There are always, of course, exceptions to the rule. For example, developmental delayed adolescents who spend all of their time with trusted adults may not need extensive time alone with the physician; however, it is best practice to check in with them alone if possible and appropriate.

Example of Interacting with an Early Adolescent

Particularly as teenagers gain emotional maturity, it is important for them to understand that their healthcare provider respects them as individuals and understands that they have autonomy in many decision-making aspects of their lives. This will help establish a trusted therapeutic relationship with the teen and allow for better use of motivational interviewing for risk reduction when necessary. One easy way to show respect is to greet the teen first upon entering the room and then asking her/him to introduce those accompanying him/her (if one does not already know them). This may not be as effective with emotionally immature teens, but as they get older, it can be very helpful. See box for sample introduction and confidentiality discussion with a new teen patient.

> Provider: Hello, you must be Mary Smith. It is nice to meet you. I am Dr. Jones. Mary (shyly) – age 14: Hi. Provider: Mary, can you please introduce me to this woman with you today? Mary: Oh, that's my mom. Provider: Thank you. Mrs. Smith, I presume? Mother: Yes. But you can call me Jane. Provider: Wonderful to meet you, Jane. I am Dr. Jones (shaking hands). Before we get started, I would like to explain to you both how we operate with teen visits. I will talk with you both, first, and hear about both of your concerns, and then I will meet with Mary alone for a bit, just to talk. For the physical exam, Mary, you may decide if you want your mother in the room. Mary: Oh, yes, please. Provider: Alright, no problem. I do want you to both know that, legally, at her age, Mary does have a right to confidentiality. So, I won't tell anyone else what Mary tells me without her permission. The only exceptions are if Mary tells me that she plans to hurt herself or someone else, or if she tells me that someone is hurting her. In those situations, I am obligated to notify other appropriate people or authorities. Do either of you have any questions?

History taking for an adolescent patient is similar to that of any other patient, particularly when the parent/guardian(s) are in the room. It is best to direct questions to the teen whenever possible and then obtain details and clarifications from the parent/guardian(s) as necessary. One can start by asking the teen if they have any concerns s/he would like to address, and then, subsequently, asking the parent/guardian(s) what they would like to address in the visit. As with any well child visit, the provider should ask about diet, exercise, screen time (including TV, computers, cell phones, video games, etc.), developmental issues (level in school, grades), and safety concerns (bike helmets, water safety, seatbelts). Regarding physical development, genetically female children should be asked about breast development and menses. All teens should be asked about pubertal hair growth. The immunization record should be reviewed for any needed boosters or updates. Once the patient's concerns and the parent/guardian(s)' concerns have been heard and understood and the past medical, surgical, medication, allergy, and family histories have been obtained, the parent/guardian(s) should be asked to step out of the room while the physician speaks with the patient alone. If there is some hesitancy or concern from the parent/guardian(s), one can explain that this is a routine part of visits with all adolescents and is recommended by all major medical associations. The parent/ guardian(s) may be further reassured that the goal of this is not to be secretive,

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but to help teenagers begin to take some responsibility for their health and their relationship with their health care provider. In almost all cases, these explanations are enough to ease parent/guardian(s)' mind. If the parent/guardian(s) are very resistant, and the teenager is relatively young, one may rarely elect to forgo the individual meeting with the teen, but should ask the family to prepare for this at their next visit. You can find a CDC handout for parents explaining the importance of individual time with the teen at this website: https://www.cdc.gov/healthyyouth/healthservices/pdf/OneonOnetime_FactSheet.pdf

Prior to the individual time with a teenager, it is a good idea to remind the adolescent about his/her right to confidentiality and the limits to that confidentiality. The primary issues to address during the individual meetings are psychosocial health issues. These include body image, mental health, sexual development and health, safety concerns, and substance use. It is important to touch on each of these issues at each visit, as teens are not seen in the office often, unless there is a problem or they need a sports or school physical. Further, adolescents are rapidly changing and answers will most certainly change from visit to visit. There are several acronyms that have been developed to help providers remember all of the areas to address. The best known is probably the HEADSSS assessment [1]. H stands for home, E is for education, A is for activity, D is for diet (body image), drugs, alcohol and tobacco, the first S is for safety, the second S stands for sex and sexuality, and finally, S for Suicide (depression). This acronym covers most important topics and is easy to remember. However, although it, in general, proceeds from least intimate to most intimate topic, home can be a sensitive topic for some teens, and school may be a safer way to start. Also, for the most part, HEADSSS focuses on risk factors, rather than acknowledging the teen patient's strengths. An alternative acronym that the author prefers [2] is shown in the side bar with letter explanation and sample questions. As is evident, this acronym begins with strengths, which is a wonderful way to begin a conversation with any patient, and the information obtained can be particularly useful if necessary to counsel the teen about risk reduction related to the other questions. Another difference in this acronym is the word *Emotion* rather than *Suicide*, which is much more neutral, and can prompt physicians to ask patients questions about rating their life and other less loaded questions first.

Psychosocial History (SSHADESS) **S – *Strengths*:** What are your strengths? What are you good at? What would your friends say that they like about you? **S – *School*:** What grade are you in? At which school? What do you like/dislike about school? Favorite subject? Friends at school? Do you feel safe at school? Any problems with bullying? Is there a trusted adult you can talk with at school? What do you plan to do after you graduate (or leave school)? **H – *Home*:** Do you feel safe at home? Do you have your own or share a room? Is there a trusted adult you can talk with at home? Is there a gun in your home? **A – *Activity*:** What do you do after school and on the weekends? How much screen time do you have? Are you involved in sports or other regular exercise? What do you do to have fun with your friends? **D – *Diet/body image*:** What do you like to eat? How often do you eat? Do you eat breakfast? How often do you eat meals with your family? Do you think that your body is about the right size, or would you like to gain or lose weight? How do you feel about your developing body? Do you see yourself as a boy or girl, both or neither? & ***Drugs/alcohol/tobacco*:** Do you know anyone who smokes or vapes? Do you smoke or vape? (Ask similar questions for alcohol and drugs.) *For teens who do use alcohol or drugs*, quantify amount and ask: Where do you use? With whom? **D – *Drugs/alcohol/tobacco (continued)*:** Do you ever drive after using or ride with someone who has used? **E – *Emotion*:** How do you feel on most days? If you would rate your life on a scale of 1–10, what number would you give your life? Why? (If less than 10), How could it be better? (If depression or low self-esteem red flags), Do you ever feel

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like hurting yourself? [Consider using a validated depression screening tool as the USPTF recommends screening for Major Depressive Disorder in all adolescents.] **S – *Safety*:** (Already partially addressed under school and home.) May talk about bike helmets, neighborhood safety, gang activity, seatbelts, never riding with impaired drivers, etc. **S – *Sexuality and Sex*:** This topic depends heavily on the sexual and emotional maturity of the teen. However, be aware that even young teens are known to sometimes be involved in sexual activity with their peers or be victims of sexual abuse. (Younger ~10–14): Do you find that you are attracted to any of your peers? If yes, are they boys or girls, both or neither? Do you have a boyfriend, girlfriend or significant other? Do you ever touch physically? Does anyone ever force you to do something that you do not want to do? As below, if appropriate. (Older ~15–21): Have you ever had sex? Do you currently? What is the gender of your partner(s)? Do you have intercourse? Oral, anal, vaginal? Barrier protection? Contraception? Do you feel safe with your partner(s)?

While the above illustrates a list of sample questions one can use, the goal is to have a conversation with teenage patients. The questions help the physician to open up the conversation. The objective of the physician should be to understand your patient's thoughts and feelings about all of these topics, in order to support them in their healthy choices and/or normalcy (most teens want to be "normal"); to help them problem solve around issues such as safety; or to motivate them to make safer, healthier choices, if they are at risk. Risk taking and experimentation during adolescence is a normal developmental process [3]. Unfortunately, reckless risk taking is a major cause of accidental death or injury in adolescents [4]. Healthcare providers can help teens understand how and be motivated to take risks in the safest possible ways. In addition to providing contraception to those teens at risk for unwanted pregnancy, healthcare providers should discuss prevention of sexually transmitted infections, including offering pre-exposure prophylaxis (PreP) to those adolescents at high risk for acquiring HIV. Physicians should also encourage adolescent patients to discuss these issues with other trusted adults as much as possible.

In addition to the questions presented, it is important to assess conflict resolution strategies for teens in their relationships, both in their families, as well as in any romantic relationships. These questions should be asked of all teens to screen for possible intimate partner violence (IPV) but also to counsel teens of all genders on healthy conflict resolution strategies. Possible questions for these issues are below.

> *What happens when there are disagreements at home? Do you feel safe in your relationships with adults and peers? Do you feel safe with your boy/girlfriend/significant other? (if appropriate) What happens when you and your girl/boyfriend/significant other argue or disagree? Do you ever feel controlled by your boy/girlfriend/significant other?*

Finally, when working with teens and their families, it is important to be aware that many adolescents may be LGBTQIA+ (lesbian, gay, bisexual, transgender, questioning [their sexuality or gender]/queer, intersex or asexual). For this reason, it is important to ask all questions around sex and sexuality with gender neutral terminology. Family physicians can help adolescents and their families understand that there is nothing wrong or abnormal about being LGBTQIA+. Unfortunately, LGBTQIA+ teens have higher rates of risky behavior, higher rates of being bullied or physically assaulted, and higher rates of depression and suicide, with transgender teens having the highest rates among all of these groups [5–9]. Acceptance and support from their family is one of the strongest protective factors for LGBTQIA+ teens, so encouraging family discussion and understanding (as much as is safe and possible) is ideal. Information for families struggling with these issues can be found at The Family Acceptance Project website: http://familyproject.sfsu.edu/home. A brief on-line training module for healthcare providers of LGBTQIA+

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adolescents can be found at http://www.lgbthealtheducation.org/wp-content/uploads/Module-4-Caring-for-LGBTQ-Youth.pdf. Other resources for caring for LGBTQA youth can be found at https://prh.org/arshep-ppts/#lgbtq-essentials.

The physical exam in adolescence need not be more invasive than the physical exam performed in other well child exams in the absence of problems or specific issues. It is still important to monitor growth, and particularly to calculate the BMI (body mass index) in order to screen for overweight or obesity issues. Obesity is a growing public health problem in children and adolescents. In 2015–2016, 20.6% of 12–19 year olds were found to be obese [10]. There is no evidence that screening adolescents for scoliosis in the absence of symptoms or problems is effective, and therefore, routine screening is not recommended [4].

The physical examination of adolescents should generally include visual inspection of the breasts and genital region for Tanner staging and observation of any abnormalities, and these aspects of the exam should be chaperoned (either by the parent/guardian or another health center staff, per the wishes of the patient). However, there is no reason to do a more invasive genital exam unless needed for diagnosis of abnormal symptoms. The USPSTF (US Services Preventive Task Force) recommends against testicular exam for screening for cancer in adolescents. Similarly, all major organizations including the USPSTF, ACOG (American College of Obstetrics and Gynecology), and the ASCCP (American Society for Colposcopy and Cervical Pathology) recommend beginning cervical cancer screening no earlier than 21 years of age, regardless of sexual history. It is important to screen sexually active teens for syphilis and HIV and for gonorrhea and chlamydia, but this can be done with urine PCR testing for genital exposure, throat swab for oral exposure, or a self-collected rectal swab for anal exposure, so there is no need for a pelvic exam unless symptoms are present, or suspicion of another problem exists [4].

Physical sexual development is generally categorized using Tanner staging. Tanner Stage 1 is the preadolescent stage. For Tanner stages, see charts below (adapted from 11). The data presented here are reported averages, but there is a wide range of "normal" and some evidence that female adolescents in the USA and other developed nations are reaching these stages at earlier ages than previously, possibly related to more available calories [12] (Tables 1 and 2).

After the physical exam, if the parent/guardian(s) are not already present, the physician can usually have them join the adolescent for the summary and closure of the visit. Prior to inviting the parent/guardian back, the physician should answer any questions the teen has and remind the patient about confidentiality and the services that they can seek without parental permission. As with other well child exams, there are several preventive and anticipatory guidance issues to consider. Regarding immunizations, the CDC (Centers for Disease Control) recommends a Tdap (tetanus, diphtheria and pertussis) booster, the first dose of meningococcal conjugate vaccine, and the HPV (human papilloma virus) vaccine series for all girls and boys at age 11–

Table 1 Tanner stages for genetic females

	Average age (years)	Breast	Pubic hair	Other
Stage II	10–11	Bud (thelarche)	Long, soft, light hair near labia	Peak growth velocity follows
Stage III	12–13	Further growth of areola and tissue, no separation	More hair and more darkly colored	Menarche may occur late in this stage
Stage IV	14–15	Areola/nipple complex separates from breast tissue – secondary mound	Hair become coarse	Menarche usually occurs in this stage
Stage V	16–17	Larger breast with single contour	Full adult distribution	Menarche may occur here

Adapted from Ref. [11]

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Table 2 Tanner stages for genetic males

	Average age (years)	Testes	Penis	Pubic hair	Other
Stage II	11–12	Testes enlarge and scrotal sac darkens	Minimal- no growth	Long, soft hair	–
Stage III	12–13	Further growth	Growth, especially in diameter	More hair and more curly	–
Stage IV	15	Further growth	Continued growth	Hair become coarser	Some axillary and facial hair
Stage V	16–17	Adult in size	Adult in size	Full adult distribution	

Adapted from Ref. [11]

12 years. A booster of the meningococcal vaccine is recommended at age of 16 years. In addition, the influenza vaccine should be administered annually. Immunocompromised teens require a different vaccination schedule. See details at https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html.

Regarding immunizations, HPV vaccine requires particular attention. The current immunization rates have improved over the last few years, but remain relatively low for both sexes. In 2017, 64.5% of girls received one dose but only 43.7% received the full series. The rates were even lower for boys, at 57.1% and 34.4%, respectively [13]. In order to increase the rates in HPV vaccination, and decrease the rates of cervical and other HPV-related cancers (including oropharyngeal, anal, vulvar, and penile cancers), primary care providers must be more effective at offering and counseling families about the vaccine. Many parent/guardian(s) believe that there is no need to vaccinate their children against a sexually transmitted disease since they are not sexually active. While physicians may educate parent/guardian(s) that vaccination should be done before exposure for maximal effectiveness, parent/guardian(s) may believe that this will increase sexual promiscuity in their teenagers. A study, however, demonstrated that there was no increase rate of sexually transmitted infections in a large group of adolescent girls after HPV vaccination [14].

Anticipatory guidance for parent/guardian(s) during the teen years is very important, but often skipped in adolescent visits. A thorough discussion of diet recommendations, exercise, and limiting screen time is warranted, particularly for teens with or at risk for obesity. There are many web-based resources for nutrition and activity in adolescence; several are available through the CDC website at http://www.cdc.gov/healthyyouth/npao/index.htm or at http://www.nutrition.gov/life-stages/adolescents/tweens-and-teens (this one has handouts for teens and parents/guardians). See Table 3 below for basic details of the American Heart Association recommended diet for teenagers [15].

In addition to a healthy diet, adolescents should participate in moderate to vigorous exercise for at least 60 min daily. The 2017 National Youth Risk Behavior Survey found that fewer than 27% of high school students were meeting these physical activity recommendations [16], so it is important for physicians to discuss physical activity with teen patients and their families. Finally, regarding screen time, the American Academy of Pediatrics recommends less than 2 h of media per day for all children. While the recommendation is that all screen time be reduced, a recent study found that only TV watching was associated with increased risk of diabetes in an at risk population of adolescents [17]. In general, however, the fewer hours spent in front of any screen, the more physically active a child will be. A healthy lifestyle, including a nutritious diet and regular exercise not only benefits adolescent physical health, but there is evidence that it is important for optimal cognitive function and emotional wellbeing as well [18, 19]. Parent/guardian(s) and teens should understand the relationship between diet, physical activity, and screen time and physical and mental health.

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Table 3 Nutritional needs of adolescents

	Girls – early adolescence	Girls – late adolescence	Boys – early adolescence	Boys – late adolescence
Calories (kcal)	1600	1800	1800	2200
Fat (% kcal)	25–35	25–35	25–35	25–35
Lean meats (oz)	5	5	5	6
Vegetables (cups)	2	2.5	2.5	3
Fruits (cups)	1	2	1.5	2.5
Grains (oz)	5	6	6	7
Fat free milk/dairy (cups)	3	3	3	3

Adapted from Ref. [15]

While counseling regarding lifestyle factors affecting obesity is very important, physicians cannot ignore the social determinants of health that affect obesity rates. Obesity is more common in low income households, and obesity rates correlate with levels of poverty. A recent article using GPS with adolescents found a complex relationship between teen's neighborhoods and their food consumption, but one clear association was a relationship between distance to convenience stores and teen fruit/vegetable consumption [20]. In addition to assisting individual adolescents and their families, physicians can work at the local and community level to address such disparities in access to healthy food and safe places to exercise and play.

Parenting strategies and discipline are topics that should be discussed with the parent/guardian(s) of adolescents whenever possible. Many parents continue to use the parenting skills they used when their children were younger. However, given that the adolescent stage of development is concerned with identity development and differentiation, these parenting strategies are often no longer very successful. The Center of Children on Families at the Brookings Institute has found that adolescents with parent/guardian(s) with certain parenting styles tend to be more successful as adults. (See below for parenting styles [21].) Adolescents with parent/guardian(s) who parent in an Authoritative style have lower risk taking behavior and higher school achievement [21]. For parent/guardian (s) with difficulties around these issues, a separate counseling appointment is sometimes necessary. The physician can also speak with parent/guardian(s) without the adolescent present if they feel more comfortable speaking about their concerns when alone. The main objective of counseling parent/guardian (s) should be to improve their authoritative parenting skills. Important authoritative parenting skills include age appropriate parental monitoring, appropriate discipline and communication of family values, as well as warmth and regard. Self-efficacy in their parenting is also important. There are many resources for parent/guardian (s) to improve their parenting skills of adolescents, particularly those of communicating with their children. An example of a helpful websites is:

A Parent's Guide to Surviving the Teen Years at kidshealth.org/parent/growth/growing/adolescence.html.

Parenting Styles **Authoritative:** High emotional support with consistent discipline ("positive parenting") **Authoritarian:** Discipline but with low emotional support ("dominating") **Indulgent:** High emotional support without discipline ("permissive") **Uninvolved:** Low discipline and low emotional support ("disengaged")

In order to be supportive of their adolescent children, parent/guardian(s) need to understand that the major developmental task of adolescence is individuation towards independence. They can be most effective when they

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communicate well and guide their children in making good choices. One simple suggestion is have parent/guardian(s) consider how they would react to their teens' situations if they were their coach rather than their parent. COACH is also an acronym parents can use. (See below.) It is very important that parent/guardian(s) know that adolescents are still greatly influenced by their parent/guardian (s) when making decisions, even if it seems that the opinions of their peers matter more [21].

COACH to Improve Parenting

C: Create Confidence
O: Observe
A: Advise
C: Calmly let them experience life
H: Help them debrief after experiences

In summary, in order to be most effective in the healthcare of adolescent patients, it is necessary to have therapeutic relationships with both the adolescent patient and her/his parent/guardian(s). Family physicians who care for all individuals in the family unit are uniquely suited to establish these relationships. Addressing adolescent health needs in a respectful and confidential way is a must, but supporting parent/guardian (s) in their relationships with their teenage children and the authoritative skills that are most effective is also necessary for optimal health outcomes for youth.

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Part V

Care of the Elderly

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Selected Problems of Aging

22

Archana M. Kudrimoti

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General Principles

Definition/Background

The population of the world is aging due to decreasing fertility and mortality rates. By 2030 one in five Americans will be above the age of 65. In the USA, the fastest-growing segment of all age groups are those aged 85 and above. Seniors disproportionately use all aspects of health services. Clinicians treating this population face the challenge not only of treating chronically ill adults but also in helping to delay or prevent the onset of chronic disease. This chapter provides information on issues that are common to this population and are valuable to the family physician who cares for these patients.

Selected Clinical Issues

Frailty

Pathophysiology

As our population ages, addressing frailty will become an essential aspect of elderly care. Frailty, defined as a chronic progressive condition with a spectrum of varying severity and heterogeneity, is a geriatric syndrome of weakness, weight loss, and low activity associated with adverse health outcomes especially in response to a stressful environment [1, 2].

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The overall prevalence of frailty in community-dwelling older adults aged 65 years and over in the USA ranges from 15%. Globally numbers range between 3.5% and 25%. This subset of the older population responds poorly to external stressors and lacks the ability to bounce back from acute illness. This in turn increases their risk of dependency. The prevalence of frailty is higher among women and African Americans. Primary frailty is due to intrinsic physiological dysregulation that has reached beyond a threshold of normal recovery. Research in recent years has shown that this results from physiological, genetic, cellular, and molecular changes in the body of the frail elder. These result in increased risk of poor outcomes, namely, falls, disability, dependence, and death (Fig. 1).

Secondary frailty is the result of complex interactions between multiple comorbidities and physiological changes during stress and aging. Among elderly people above 65 years of age, 75% suffer from three or more chronic conditions. Chronic conditions, including coronary artery disease, congestive heart failure, hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, arthritis, cancer, diabetes, and HIV/AIDS, all increase the risk of disability and frailty. In both primary and secondary frailty, changes in the body occur, leading to decreased muscle mass (sarcopenia), loss of muscle strength, slowed motor performance (such as walking speed), decreased physical activity, worsened exercise tolerance (low energy or fatigue), and inadequate nutritional intake.

Diagnosis

In the clinical setting, the presence of frailty can be assessed by identifying at-risk elders through a detailed history, physical examination, and Comprehensive Geriatric Assessment. There are many validated tools available to use in clinical settings to screen for frail elders [3, 4] (See Table 1). There are two prominent models that form the basis of assessment tools. Frailty Phenotype tools are based on the five phenotypic criteria, and frailty index tools estimate the accumulation of deficits that occur due to aging process [5]. The first manifestation of frailty tends to be weakness, slowed walking speed, and/or decreased physical activity. Walking speed has been shown to predict

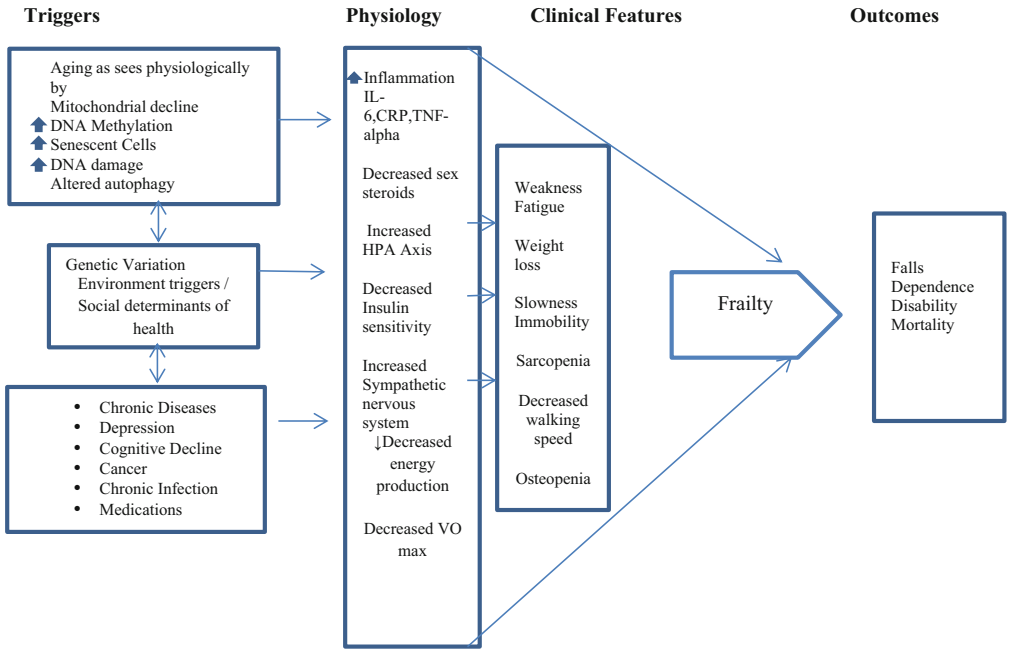


Fig. 1 Model for frailty

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Table 1 Frailty assessment tools

Frailty assessment tool	Content
Frailty Phenotype [6]	Uses signs and symptoms to assess by predefined criteria – Frail if three of five criteria present
Clinical Frailty Scale [7]	Uses physical and functional indicators – 7 point scale to quantify degree of frailty
Vulnerable Elders Survey [8]	Thirteen questions, considers age, self-rated health, limitations in physical function, and functional disabilities- identifies at-risk community dwellers for health deterioration
Groningen Frailty Indicator [9]	The GFI is a validated, 15-item questionnaire with a score range from zero to fifteen that assesses the physical, cognitive, social, and psychological domains. A GFI score of four or greater is considered the cutoff point for frailty
Edmonton Frail Scale [10]	Multidimensional assessment instrument that includes the timed-up-and go test and a test for cognitive impairment
SHARE-FI Frailty Instrument [11]	Measures five items including grip scale – Has a web-based calculator
Tilburg Frailty Indicator [12]	Has two parts, part A measures life course determinants and multi-morbidity, and part B measures physical, social, and psychological domains of frailty
Comprehensive Geriatric Assessment [13]	Standard CGA-good correlation with clinical frailty scale
Frailty index (deficit accumulation index) [14]	The frailty index is composed by a long checklist of clinical conditions and diseases. Score is based on total accumulated deficits
FRAIL Scale [15]	Easy to remember F = fatigue, R = resistance (unable to climb one flight of stairs), A = ambulation (inability to walk one block), I = more than 5 illness, L = loss of weight (5%)

mortality and mobility disability and is a good screening marker. Frail elders meet three or more of five phenotypic criteria: weakness as measured by low grip strength (based on gender and body mass index), slowness by slowed walking speed (takes greater than 6–7 s to walk 15 ft), low level of physical activity (expends less than 270 kcal/ week for females and less than 383 kcal/ week for males based on activity scale), low energy or self-reported exhaustion, and unintentional weight loss (more than 10 lb. in a year) [1, 2]. Disability is measured by impairment in activities of daily living (ADL) and instrumental activities of daily living (IADL) (Table 2), and comorbidity is defined by the presence of two or more diseases. Frailty is a distinct entity and so can sometimes exist without the presence of disability or chronic comorbidities. Currently efforts are underway to identify biomarkers to identify frailty.

Management

Frailty is managed by a team-based, multi-disciplinary approach targeting biological, socio-behavioral, and environmental stressors and is associated with improved outcomes especially with respect to polypharmacy, falls, functional status, decreased nursing home admission, and mortality [16]. Preventing and minimizing immobility and maintaining physical activity and muscle mass are critical in older adults at risk of frailty. Resistance, or strengthening exercise supplemented by aerobic exercise and balance training [17] (e.g., tai chi) and nutritional support, particularly protein supplementation, appears to be important to both the prevention and management of frailty. Decreasing the stress of environments such as hospitals by reducing iatrogenic adverse events and polypharmacy during acute illness is also important. The role of micronutrient supplementation and hormone replacement therapy is not clear [18]. Addressing depression and various physical comorbidities is important to frailty management [19, 20]. Prescribing various appetite stimulants and anabolic agents to undernourished older adults needs further investigation. Recent studies with nutritional interventions like specific nutritional supplement formula; daily food fortification with protein supplement; nutritional education and counseling; and supplementation of micronutrients, including vitamin D,

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Table 2 Definitions of ADLs and IADLs

Activities of daily living (ADLs)	Instrumental activities of daily living (IADLs)
Ability to perform basic self-care tasks: *Dressing* – Ability to dress oneself appropriately *Eating* – Ability to self-feed *Ambulating* – Ability to move in one's environment *Toileting* – Ability to use toilet facilities *Hygiene* – Ability to clean oneself, including hair and teeth	Ability to use instruments and interact with the environment to perform tasks necessary for independent function: *Shopping* – Ability to obtain necessary terns for care (food, clothing, hygiene needs) *Housekeeping* – Ability to keep environment clean *Accounting* – Ability to manage money and simple finances *Food preparation* – Ability to prepare foods for eating *Transportation* – Ability to use modes of transportation to get necessary items

omega-3 fatty acids, and multivitamins have reported mixed results. The management approach should consider issues that are particular to each individual, including interactions among conditions, and treatments, the patient's own preferences, goals, and prognosis as well as the feasibility of each management decision and its implementation [18].

Although frail elderly patients as a group have higher rates of morbidity and mortality, it is important to recognize that many frail elders will live for a number of years at a functional level. Key considerations for prevention of frailty include monitoring physiologic reserve, performing regular exercise to prevent chronic muscle loss, preventing acute illness (vaccinations), increasing physiologic reserve before anticipated loss (prehabilitation), and removing obstacles for smooth recovery (comprehensive geriatric evaluations).Understanding any functional losses that frail elderly may have sustained and pairing their needs with an appropriate level of services is important to maintain their quality of life. Early referral to palliative services when indicated may prolong survival and improve quality of life.

Constipation

Constipation is one of the most common gastrointestinal disorders seen in elderly. In adults older than 60 years, the prevalence is 33%, whereas the overall prevalence among adults of all ages is about 16%. Physicians typically define chronic constipation as infrequent bowel movements, usually less than three per week, for at least three of the prior 12 months. Patients may complain of a myriad of symptoms including hard stools, feeling of incomplete evacuation, abdominal discomfort, bloating and distension, excessive straining, sense of anorectal blockage during defecation, and the need for manual maneuvers and the use of laxatives [21, 22].

Types and Risk Factors

Constipation may occur in isolation or due to specific disorders. Primary constipation can be divided into three main types based on colon transit time and ROME 3 symptom criteria: normal transit, outlet dysfunction or defecatory disorder, and slow transit constipation [21]. There can be overlap of these primary types of constipation. The self-reported prevalence of secondary constipation increases with age and occurs more commonly in females than males. Less exercise, a sedentary lifestyle, diseases that create immobility, and the use of a variety of medications are the most significant risk factors in the elderly for secondary constipation (Tables 3 and 4).

Evaluation

Evaluation of constipation begins with a detailed history and physical examination, including a visual survey of perianal area, a digital rectal examination, and a detailed medication review. This initial assessment will help to identify secondary causes of constipation . Further diagnostic tests are directed toward symptoms and history and physical exam findings to rule out organic causes. Primary constipation is usually diagnosed after initial workup identifies no obvious etiology. The presence of any concerning symptoms such as bleeding per rectum, weight loss, and abnormal

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Table 3 Diseases associated with chronic constipation in the elderly

Neuropsychiatric disorders	Non-neuropsychiatric disorders
Multiple sclerosis	Hypothyroidism
Parkinson's disease	Diabetes mellitus
Spinal cord injury	Hypercalcemia
Autonomic neuropathies	Hypokalemia
Depression	Systemic sclerosis
Stroke	Obstructing colonic lesions like cancer
	Dehydration

Table 4 Medications associated with constipation

Anticholinergics – Tricyclic antidepressants
Anticonvulsants
Antihypertensives – Calcium channel blockers diuretics
Anti-Parkinsonsian drugs
Opiates
5-HT $_3$-antagonists
Nonsteroidal anti-inflammatories
Chronic laxative abuse
Bismuth, iron, lithium, iron, aluminum antacids

test results like anemia should prompt urgent direct visualization of colon. Colon transit study or manometric evaluations may be indicated in refractory cases of constipation [22].

Management of Constipation

Nonpharmacological Management

Most elderly will improve by increasing physical activity, fluid intake, increasing fiber slowly to 25–30 g in their diet, and the cessation of any offending medications. It is important to remind individuals to respond to the urge to defecate after drinking warm, caffeinated beverages in the morning and to develop a daily routine for toileting. Foods high in soluble fibers such as grains, bran, nuts, beans, vegetables, or fresh fruits will help by adding bulk to the stool.

Pharmacological Management

When lifestyle, dietary changes, and nonpharmacological interventions are insufficient to ameliorate symptoms, a variety of over-the-counter and prescription medications are available to treat constipation. A stepwise approach with initial bulking agents and an osmotic laxative should be considered before adding stimulants (Table 5). Bulking agents cause increases in stool volume, a decrease in colon transit time, and an improvement in stooling consistency. Osmotically active agents are nonabsorbed agents whose main side effects are increased bloating and gas. Stimulants alter colonic motility and can alter fluid and electrolyte transport into the stool. They should be restricted in their use to two to three times a week to prevent overstimulation and atony of the bowel. The last resort for severe constipation is the addition of rectal suppositories and/or enemas to stimulate colon evacuation. In elderly with cardiac and renal problems, use of phosphate enemas more than the recommended dose (one enema in 24 h) can lead to electrolyte abnormalities, dehydration, and rarely death. Lubricants are avoided in elderly as they can cause lipoid pneumonia if aspirated as well as anal leakage.

Newer agents like chloride channel activators (lubiprostone) and guanylate cyclase C activator (linaclotide) act at the receptor level in the gut and increase intestinal fluid, accelerated stool transit, and relaxation of the smooth muscle and may be indicated in select cases of chronic constipation. Serotonin 5-HT4 receptor agonists (e.g.,

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Table 5 Drug therapy for constipation

Drug groups and specific medications	Common doses	Comments
Bulk agents		Effective at 12–72 h, inexpensive, causes gas and bloating
Bran Methylcellulose (Citrucel) Psyllium (Metamucil, Konsyl) Barley malt extract Calcium polycarbophil (FiberCon)	1 cup/day 1–4 tbsp./day 1–4 tbsp./day 12–32 g bid 1 tab qd-qid	
Lubricants		
Mineral oil	Contraindicated in elderly	
Osmotic/ hyperosmolar agents		Effective in 24–48 h, nonabsorbable, treats moderate to severe constipation PEG effective in 1 h
Lactulose (Cephulac) Sorbitol (70%) Polyethylene glycol (Metamucil)	15–30 ml qd-bid 15–30 ml qd-bid 6–25 g once per day	
Stimulants		Most effective, most work within 1 h, senna takes 8–12 h, long-term uses of anthraquinones causes melanosis coli, GI cramping
Anthraquinones-senna (Senokot) Bisacodyl (Dulcolax) Glycerin	Two tablets once daily to four tablets twice daily 10 mg suppositories or 5–10 mg by mouth up to three times/week Suppository; up to once daily	Rectal irritation
Saline laxative		Effective in 1–3 h, Magnesium toxicity
Magnesium (milk of magnesia)	15–30 ml once or twice daily	
Enemas		Effective within 30 min, last resort in healthy patients; used frequently in combinations with stimulants in patients who are demented, hospitalized, or on chronic narcotics Mechanical trauma, electrolyte problems
Tap water Phosphate enema (Fleet) Soap suds enema Mineral oil retention enema	500 ml per rectum 1 unit per rectum 1500 ml per rectum 200–250 ml per rectum	
Secretagogues		Opioid-induced constipation diarrhea, nausea headache
Lubiprostone (Amitiza) Linaclotide (Linzess)	24 mcg BID 145 mcg once daily	
Serotonin 5-HT4 receptor Agonists (prucalopride)	2–4 mg once daily	Approved by FDA, also available in Canada and Europe

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prucalopride) act by increasing intestinal motility and are available in Europe and Canada [23].

Sleep-Related Disorders in Elderly

Older adults consider quality sleep an essential part of good health [24]. More than half the elderly have sleep complaints. There is a common misconception that sleep disruption is an expected phenomenon of aging. Higher prevalence of sleep disruption is noted in the elderly as it is related to coexistent physical and psychosocial conditions and not solely due to physiological changes. It appears that there is bidirectional relationship between sleep disorders and multiple comorbidities and psychiatric disorders [25]. The most common sleep complaints among older adults are difficulty falling asleep, nighttime awakening, early morning awakening, and daytime sleepiness. Certain sleep disorders do increase in prevalence with age, such as sleep-related breathing disorders (i.e., sleep apnea) [26], periodic limb movement disorder [27], restless legs syndrome, and circadian rhythm sleep disorders. At least one-half of community-dwelling older adults use OTC and/or prescription sleeping medications [28].

Compared with younger adults, older adults generally take longer to fall asleep and have more nighttime wakefulness and more daytime napping. This is due to intrinsic age-dependent changes and interactions between circadian arousing processes and the homeostatic sleep drive. An earlier bedtime and earlier wake time are also common due to advanced circadian rhythms and reduced amplitude of circadian rhythm. Older adults also have less N3, or slow-wave, sleep (which is the deeper stage of sleep) than younger adults and increases in light stages of sleep [29].

Sleep-related disorders can be identified by routinely asking simple screening questions related to sleep habits, snoring, sleep quality, leg movements in sleep, and daytime sleepiness or fatigue. Assessment of coexisting medical problems and medications that affect sleep should be considered. Polysomnography may be indicated when sleep apnea, periodic sleep disorders, or narcolepsy is suspected. Wrist actigraphy can be used in identifying circadian rhythm disorders and in nursing home residents, in whom traditional sleep monitoring can be difficult to obtain [20].

Management of sleep-related disorders is guided by the specific diagnosis and any associated medical comorbidities. Sleep hygiene measures can help with milder insomnia. The strongest evidence currently supports cognitive-behavioral therapy for chronic insomnia which generally combines stimulus control, sleep restriction, and cognitive restructuring [20]. Short-term hypnotic therapy can be considered, but long-term use has been associated with increases in adverse events like falls [30], cognitive impairment, and impaired driving [31, 32]. Obstructive sleep apnea (OSA) is a treatable condition that is associated with cardiovascular disease, including hypertension, stroke, myocardial ischemia, arrhythmias, cardiovascular events, and all-cause mortality [33]. OSA is also associated with motor vehicle crashes, and there is some evidence suggesting a link to cognitive impairment [34]. Older patients whose sleep apnea is associated with congestive heart failure or respiratory disease should be referred to a sleep specialist.

Social and Functional Issues

The vast majority of Medicare beneficiaries have one or more chronic conditions and geriatric syndromes, which are defined as unique, multifactorial health conditions in elderly that increase their risk of dependency and disability. Our healthcare system is organized in such a way that most sites of care such as the hospital, outpatient clinic, and nursing homes work in silos and there is not much incentive to improve care coordination [35]. Therefore, innovative cost-effective models that consider comprehensive geriatric evaluations and those that improve the quality of care and safety of the elderly should be developed and financed by current healthcare system [36] (Fig. 2).

In acute care settings, systematic approaches using multicomponent multidisciplinary

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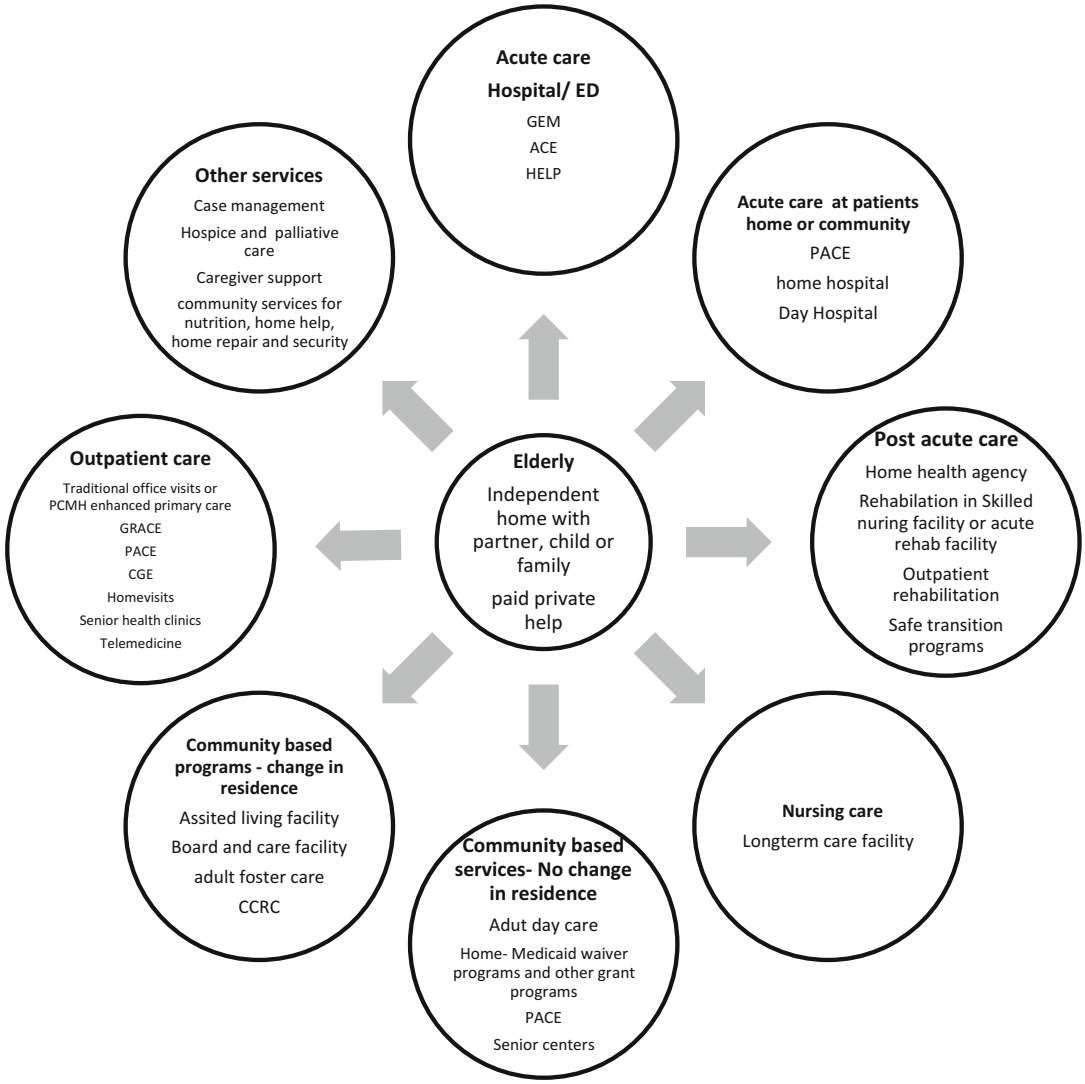


Fig. 2 Services available for elderly across various healthcare settings. *GEM* geriatric evaluation and management, *ACE* acute care of elderly, *HELP* hospital elder life program

interventions decrease morbidity in hospital and improve functional outcomes [37–39]. In some situations hospital at home provides safe, economic, and effective alternatives to inpatient care in the community [20, 36]. Targeted interventions that improve care transitions before and after discharge, the use of home health services, caregiver support, case management, and comprehensive discharge planning that includes follow-up, medication reconciliation, and education have all been shown to reduce inhospital readmission and improve clinical and functional outcomes [36, 40].

Program of All-Inclusive Care for the Elderly (PACE) [41, 42] is a model of care that provides inpatient, outpatient, and long-term services to frail community-dwelling adults requiring more rigorous c, typically only available in a nursing home setting. Interdisciplinary teams provide care across the continuum, thereby catering to complex medical and social needs of these elderly individuals.

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Outpatient comprehensive geriatric assessment (CGA) [37] and geriatric evaluation and management (GEM) [36] are supplemental services designed to identify all of a person's health conditions affecting their physical, cognitive, functional, and social capabilities and also to help with development of comprehensive treatment plan. Geriatric Resources for Assessment and Care of Elders (GRACE) is a patient centered medical home-based model with enhanced geriatric care which provides home-based CGA by an interdisciplinary team, who coordinate complex healthcare needs with the patient's primary care provider and community liaison [40, 42].

Community-Based Assistive Services and Living Arrangements

The population of older adults is characterized by heterogeneity across measures of health status, functioning, and socioeconomic position. The options available to a particular individual are dependent on many variables including the seniors' specific needs, their caregiver support in terms of family and friends, their financial and insurance status, available assistive services, and living arrangements. For the physician, an important goal is to assist the patient in finding appropriate services and living arrangements (Fig. 2) [20, 43].

Assistive Services

Informal support for seniors comes from family and friends. Formal support services are part of every community. There are a variety of formal assistive services designed to support seniors who are living in noninstitutionalized settings. Support services come from both governmental organizations and private organizations. Information and referral services are available to find the types of services that people need (Table 6).

Alternative Living Arrangements

Many seniors find themselves in need of living arrangements other than the single family home/apartment because of failing health. There are a variety of options, depending on the level of services needed.

Independent living facilities – Independent living facilities (ILFs) are for the senior who needs minimal services but prefers to have them centralized. Such housing usually is an apartment or a bungalow that is associated with a facility providing services in a centralized location. Usually ILFs provide for a congregate meal service, exercise facility, group activities, and a group transportation system. Many of these facilities provide for an easy transition to a more intensive assisted living mode.

Board and care facilities – The board and care facilities are also called group homes or residential care facilities. These are living arrangements in which a number of unrelated seniors live together providing for a reduced cost of services and greater care supervision. The residents can have their own room, or share a room, and have access to a cooperative living room, dining room, and kitchen. There is nonprofessional staff support at these facilities that does the housecleaning and meal preparation and can assist residents in the taking of medication. These facilities are frequently licensed by the state.

Assisted living facilities – Assisted living facilities are growing in popularity. They are also known as personal homes, residential homes, and domiciliary care. An assisted living facility offers an independent living arrangement with 24 h support from licensed professional staff. Medication administration and management can be directed by either nonskilled or nursing staff depending on state license requirements. They have fewer regulations and are mostly funded by private long-term care insurance. Costs are not reimbursed by Medicare except in a few states. Usually people share living rooms, dining rooms, and recreational facilities but live in their own apartment-like room. This living arrangement is intended to provide seniors with increasing help from staff as they age while they remain in the same environments.

Continuing care retirement communities (*CCRCs*) – CCRCs are all-inclusive facilities that provide the levels of care necessary for the aging individual. They require substantial

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Table 6 Formal community-based support services for seniors

Community-based services	Description
Senior centers	Central location for group activities for seniors such as games, crafts, health fairs, etc.; usually has a congregate meal program
Adult day care	Provides daytime supervised activities for seniors in a group setting; some can accommodate patients with dementia. Nonskilled custodial care to custodial car not covered by Medicare
Day hospitals	Provides daytime supervised activities for seniors in a group setting plus medical services (usually multidisciplinary rehabilitation services or nursing services for parenteral medication). Covered by Medicare like home health services
Nutrition programs	Provides meals to seniors; can be at congregate sites such as day care or senior centers; can be home delivered program such as meals-on-wheels
Housekeeping services	Provides simple housekeeping services such as house cleaning, washing, shopping, or food preparation
Home repair services	Provides necessary home repair services such as installation of safety equipment (bath railing, locks), repair of steps or simple plumbing or electrical needs
Security services	Provides for easy contact to emergency services; commonly a necklace or button that contacts local emergency room
Telephone contact services	Provides for a daily telephone call to ensure that the individual is in no need
Transportation services	Provides transportation for seniors into the community; sometimes limited to appointments for healthcare needs
Case management	Provides a coordinator of care for a senior who can assist in financial and social service needs
Respite care	Provides for short-term care for a senior so that a live-in caregiver can have a break (respite) from care

financial resources that are typically funded through upfront "entry fees" and a fixed monthly expense, or a variable monthly expense depending on the level of services needed. Most provide for independent living, assisted living, and more supervised living including a skilled nursing facility. Financing is mostly private, but some facilities may have Medicare- or Medicaid-funded beds for skilled care.

How to Help Seniors Understand Medicare

Medicare Structure

Medicare is federal health insurance that is administered by the Center of Medicare and Medicaid Services (CMS) for people 65 or older, people under 65 with certain disabilities, and people of any age with end-stage renal disease (ESRD) requiring dialysis or a kidney transplant. It was enacted into law in 1965 and is currently the nation's largest source of payment for medical care, insuring almost 54 million beneficiaries.

Medicare comprises four benefits. Medicare Part A covers hospital, skilled nursing home, home health, and hospice services. Medicare Part B covers physicians, nurse practitioners, social workers, psychologists, therapists, laboratory tests, and durable medical equipment. Medicare Part D covers some of the cost of prescription medications. Medicare Part C provides the benefits offered under Medicare Parts A and B through Medicare Advantage (MA) plans, which are managed care plans. Most MA plans also offer Medicare Part D benefits. Medigap supplemental insurance plans are available that cover Medicare Part A and Part B deductibles and coinsurance costs [44]. Medicaid is a joint federal and state program that provides health insurance (including long-term custodial care in nursing homes) to people of all ages who have low incomes and limited savings [45].

The Affordable Care Act (ACA) of 2010 laid out several changes to the financing, coverage, and costs of healthcare for older adults. Some of the major changes include creation of the Center for Medicare and Medicaid Innovation (CMI),

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which has been charged with testing and implementing new care and payment models such as the Accountable Care Organization and the Patient-Centered Medical Home, partial closure of the coverage gap in the Medicare Part D, extended coverage for preventive care services, and expansion of Medicaid (32/50 states as of September 2017) in which many more Medicare beneficiaries will be qualified as dually eligible, eliminating many of their out-of-pocket expenditures.

Although Medicare spending is on a slower upward trajectory now than in past decades, the aging of the population, growth in Medicare enrollment due to the baby boom generation reaching the age of eligibility, and increases in per capita healthcare costs are leading to growth in overall Medicare spending. At the same time, recent legislative changes, including repeal of the ACA's individual mandate, have worsened the short-term outlook for the Medicare Part A trust fund and have led to projections of higher Medicare spending in the future.

Medicare Finances

In 2018, Medicare accounted for 15% of the federal budget and 20% of national healthcare spending, 30% on prescription drugs, 23% on physician services, and 25% of hospital payments. 85% of the funding comes from people younger than 65 years old through taxes and interest on the Medicare trust fund. Only 15% comes from monthly premiums, deductibles, and co-payments. Total Medicare benefit payments for 2018 were 731billion dollars [45]. Approximately 85% of patients with Medicare have some form of supplemental insurance to help pay for deductible costs, co-payments, and uncovered expenses (especially prescription drug costs). Fifteen percent of patients have Medicaid supplemental insurance, 35% have an employer-sponsored plan, 25% have purchased a private supplemental plan (so-called Medigap policy), and 10% have supplemental plans through a variety of public (state and federal) programs. In 2013, the average Medicare beneficiary spent $ 5503 out of pocket. This Table 7 includes premiums for Medicare and other types of supplemental insurance and costs incurred for medical and long-term care services [46, 47].

Covered Services

Medicare is an extensive insurance plan with coverage extending from hospital to home and from physicians to therapists. Its coverage is complex and subject to a variety of deductibles and co-payments (Table 7). Neither Part A nor Part B of the Medicare program covers routine dental or foot care, hearing aids, eyeglasses, orthopedic shoes, cosmetic surgery, acupuncture, custodial nursing home care, or care in foreign countries. The preventive services that are 100% covered are yearly wellness visits, a fecal occult blood test, pap smear, Herpes zoster vaccination, screening mammogram, blood tests for diabetes, cardiovascular disease, influenza and pneumococcal vaccinations, glaucoma screening, sigmoidoscopy or colonoscopy or barium enema, measurement of bone mass, hepatitis B vaccination, and medical nutrition therapy for diabetes and kidney disease [44].

Assessing Older Drivers

Currently, motor vehicle injuries are the leading cause of injury-related deaths among 65- to 74-year-olds and are the second leading cause (after falls) among those aged 75 to 84 years. Older adult drivers have the highest fatality rate per crash and per mile driven among all age groups except for those below 29 years. Driving is a cornerstone issue for many seniors as it provides access to shopping, medical services, food, and socialization. The inability to drive may increase the risk of social isolation and negatively affects well-being.

Inquiry about driving should be routine part of history taking. The initial screen should include review of medications and an assessment of any medical illness that might affect driving ability. A collateral history from family members about unsafe driving behaviors or traffic violations may be required. Those at risk should have driving-related factors assessed. These include vision, cognition, and somatosensory skills.

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Table 7 Health coverage in elderly at a glance

Plan	Medicare Part A	Medicare Part B	Medicaid	Medicare Part D	Medicare Part C	Medigap
Coverage	Hospitals – First 60 days per benefit period Postacute care in skilled nursing facility 100 days Hospice Home care ("medically necessary") Durable medical equipment(80% covered)	Home care ("medically necessary") Durable medical equipment Diagnostic laboratory tests Diagnostic imaging tests Physicians, nurse practitioners Outpatient PT, OT, ST Outpatient services, supplies Emergency care Ambulance services Preventive services Outpatient mental healthcare	Hospital as well as outpatient and preventative services as outlined in part B. vary state to state	Prescription plan for generic and brand name drugs – Plan pays 75%, Between $3750 to $8418 beneficiaries will pay 44% of the cost of generic medications, Above that Catastrophic coverage by Medicare	Covers hospital part A and outpatient services part B and drug benefits May have additional preventive services	Medicare supplemental insurance plan Pays co-pays and deductibles for Medicare part A and part B Can choose own provider PPO and HO
Funds	Federal payroll taxes	Federal income tax and premiums	State and federal tax dollars	Insurance plan and Medicare	Private insurance plan	Private insurance plans
Monthly premium	None	144–491 $ per month based on income	None	Varies 12–70 $ Plus plan premium based on income	Varies	Varies by plan and health status
Deductible	$ 1408 (may be covered by secondary insurer)	183 $ per year	None	Max of 435$	Varies	Varies
Other expenses	Pay partial or full after 60 days (unless dual eligible)	20% co-payments for some services	20% co-pay in some states	Co-pay and co-payments varies	Varies	
Comments	Hospice-patient makes co-payments of $5.00 per outpatient prescription and 5% of cost of respite care		Major payor for nursing home care in many states	.	Medicare advantage Can choose own provider PPO or HMO	Does not cover vision, dental care or LTC

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Table 8 Potential or mild functional losses associated with increased driving risks

Cognitive loss	Visual-spatial losses more important than memory in early disease Slowed central processing of information ("slowed reaction time") MOCA (Montreal Cognitive Assessment) $\leq$18; Mini-Mental Status Examination (MMSE) $\leq$ 24; Trail Making Test $\geq$180secs, Maze Test $\geq$60secs
Motor loss	Loss of grip strength and wrist function Limitations in rotation of neck Limitation in upper and lower extremity motion/strength Rapid walk or get up and go test $\geq$9 secs
Sensory loss	Visual loss – Visual fields, central acuity, night vision, and increased glare Hearing loss – Especially bilateral hearing loss Patients with combined visual and hearing loss at highest risk
Loss of consciousness	Any seizure disorder Medical diseases (cerebrovascular, cardiac arrhythmias, diabetes, medication use, alcohol use) that have caused loss of consciousness within last year

Table 8 lists the most commonly cited causes of potential or mild functional losses correlated with driving impairment. Licensing, and testing, and mandatory medical reporting requirements vary from state to state in the USA. Physicians often play a key role in identification and referral of potentially unsafe drivers [48].

Once the physician has determined that the individual elder is at risk, then a discussion should ensue with the patient and their family about reasons for restricting driving and possible evaluation and remediation through driving rehabilitation services or adult driving classes [49]. In many states, the Department of Motor Vehicles has a driving competency assessment program that requires seniors to take written and performance tests to determine continued licensure. In states where this is unavailable, it is important to consider assisting the patient and family with alternate modes of transportation and available services to help compensate for the loss of driving independence. Ongoing assessment at follow-up is crucial to identify depression, isolation of the patient, and caregiver stress.

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Common Problems of the Elderly

23

Karenn Chan, Lesley Charles, Jean Triscott, and Bonnie Dobbs

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Urinary Incontinence

A standardized definition of urinary incontinence (UI) by the International Continence Society states that UI is the complaint of involuntary loss of urine, which is objectively demonstrable and is a social or hygienic problem [1]. Based on population studies, the prevalence of UI ranges from 9.9% to 36.1%, and prevalence is often twofold higher in older women versus older men [2]. UI is underreported, with an estimated 50% of patients not seeking help. This may be due to embarrassment or the belief that UI is a normal part of aging. There are significant clinical, psychosocial, and financial impacts associated with UI, including depression, anxiety, sexual dysfunction, work impairment, social isolation, dependence on caregivers, and reductions in quality of life [3].

In the elderly, bladder capacity and force of contractility decrease as a result of the aging process while the post-void residual (PVR) volume may increase [4]. There also may be uninhibited bladder contractions. These physiological changes do not cause UI but are predisposing factors for UI. There also are age-associated changes in vasopressin and atrial natriuretic hormone that lead to the elderly excreting most of their fluids later in the day and at night, resulting in one to two episodes of nocturia [5].

Types of Urinary Incontinence

When evaluating a patient with UI, a key initial step is determining if the condition is due to a transient or an established cause. A transient cause should be sought because treatment will usually restore continence.

Transient Urinary Incontinence

Transient causes of UI probably account for 33% of cases in the community-dwelling elderly, around 50% of cases of hospitalized elderly patients, and a significant number of patients in long-term care [1]. For acute-onset cases of UI, there often is a treatable cause. The mnemonic "DIAPPERS" is used to recall possible causes of transient UI [6]:

- *D*elirium
- *I*nfection – urinary (symptomatic)
- *A*trophic urethritis/vaginitis
- *P*harmaceutical/ *p*rostate
- *P*sychological, especially depression
- *E*ndocrine (or excess fluid intake/output)
- *R*estricted mobility
- *S*tool impaction

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If a treatable cause is found, action should be taken to remedy the problem.

Established Urinary Incontinence

With established UI, no reversible cause is identified, and the incontinence is chronic. There are five major types of established UI to consider. These are urge, stress, overflow, functional, and mixed incontinence.

Urge incontinence (overactive bladder) is the most frequent type of established UI in older adults [5]. Symptoms include a sudden, uncontrollable need to void. Urge incontinence can result in the loss of large or small amounts of urine, often on the way to the washroom. There also may be symptoms of frequency, nocturia, and enuresis associated with urge incontinence. Urge incontinence is the result of abnormal detrusor muscle contractions.

Stress incontinence is losses of small volumes of urine with increases in intra-abdominal pressure (e.g., sneezing, coughing, lifting). There are two key types of stress incontinence: anatomic stress incontinence and intrinsic sphincteric deficiency. Anatomic stress incontinence is caused by anatomical changes resulting in bladder and bladder neck hypermobility. These changes often are associated with vaginal childbirth or postmenopausal status. Anatomic stress incontinence is commonly seen in older women in ambulatory clinic settings and long-term care [5]. Risk factors include pelvic prolapse, cystocele, or urethrocele. Intrinsic sphincteric deficiency, the second type of stress incontinence, is caused by functional damage to the urethral sphincter mechanism. This may be the result of prior pelvic or bladder surgery, radiation, or trauma.

Overflow incontinence is the third major type of incontinence. Overflow incontinence is thought to be the second commonest type of established UI in older men. With overflow incontinence, the bladder cannot empty properly and becomes overdistended. Presenting symptoms include dribbling, weak urinary stream, intermittency, hesitancy, straining, frequency, and nocturia resulting in the loss of continual, small volumes of urine. The most common cause of overflow incontinence in men is bladder outlet obstruction from prostatic enlargement (e.g., benign prostatic hyperplasia or prostate cancer). In women, cystoceles or uterine prolapse can less commonly cause obstruction incontinence. Urethral or bladder neck stricture or stone also may cause overflow incontinence in women. A second cause of overflow incontinence in both sexes is detrusor hypocontractility which may be from a neurogenic or non-neurogenic cause. With age, the detrusor may become fibrotic and replaced by connective tissue leading to impaired contractility. Neurogenic causes include neuropathy from diabetes mellitus, pernicious anemia, alcoholism, and mechanical damage to the spinal nerves from a herniated disc, spinal stenosis, and/or a tumor.

Functional incontinence, the fourth type of UI, occurs in patients with normal genitourinary functioning. It may result from a decline in physical or cognitive functioning or may be the result of psychiatric illness. These changes affect the person's ability to void independently.

Mixed incontinence, the final type of UI, typically is a combination of urge and stress incontinence. As such, mixed incontinence shares both the causes and symptoms of both stress incontinence and urge incontinence.

Evaluation of Urinary Incontinence

All patients with UI must be evaluated for any transient-reversible causes. This should include a history, physical examination, and urinalysis. The history will cover the UI symptoms including duration, frequency, timing, precipitants, and the amount of urine lost. Associated symptoms such as frequency, urgency, nocturia, dysuria, hesitancy, straining, poor stream, and hematuria should be ascertained. In order to exclude potentially serious underlying conditions, patients with UI should be asked about onset of incontinence, abdominal or pelvic pain, hematuria, lower extremity weakness, changes in gait, cardiopulmonary and neurologic symptoms, weight changes, and/or mental status changes. Alcohol and caffeine intake also should be noted. Additional history should be obtained regarding

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sensation of prolapse, prior surgery, urinary tract infection symptoms, parity and mode of delivery, vaginal symptoms, bowel habit, and history of constipation. A structured medication review also should occur. The effect of UI on quality of life should be determined. In frail older adults, asking about functional status, mood changes, mobility changes, changes in cognitive status, and medication changes is especially important [7].

The physical examination includes abdominal, neurologic, and genitourinary tract examinations. The bladder must be palpated. The family physician should assess both cognitive function and nerve roots S2–3 during the neurologic examination. In men, the genitalia should be examined to look for abnormalities of the foreskin, glans penis, and perineal skin. A rectal examination should be performed, testing for perineal sensation, sphincter tone, fecal impaction, and prostatic enlargement. In women, a pelvic examination should be undertaken to assess perineal skin and muscle tone and to determine if there is pelvic prolapse or a pelvic mass. The cough stress test should be performed to assess if there is urine loss with a full bladder [8]. Examination also should include a post-void residual (PVR).

The type of UI should be identified. If the cause of UI is still unclear, a daily voiding diary may help to clarify the type and severity of the UI. Referral to a specialist should be considered in these cases. Referral to a continence specialist or further investigation with urodynamics could be considered if the diagnosis is uncertain or if treatment has not been successful. If there is persistent hematuria without infection, the patient may require cystoscopy. Referral to a specialist could be considered if surgery is being contemplated to clearly identify the underlying type of UI (e.g., transurethral resection of the prostate or gynecological surgery).

Treatment of Urinary Incontinence

There are three main approaches to treatment of UI: behavioral, pharmacological, and surgical [5]. Behavioral techniques include toilet assistance, bladder education/retraining, pelvic floor muscle exercises, biofeedback, and electrical stimulation. Toilet assistance can include scheduled toileting or prompted voiding. Bladder education involves delayed and timed voiding, urge suppression, and fluid/diet alterations. Bladder training may be useful for urge and stress UI. Prompted voiding often is used in frail or cognitively impaired patients. For stress incontinence, pelvic floor muscle exercises or Kegel exercises are useful. Vaginal cones (weights that are inserted into the vaginal vault and held in place) also can be used to strengthen the pelvic floor muscles. Patients should consume six to eight cups of fluid per day and limit caffeine and alcohol intake. Non-pharmacologic treatments for overflow incontinence include intermittent catheterization, indwelling urethral or suprapubic catheters, external collection systems, and protective undergarments. Chronic indwelling catheters increase frequency of symptomatic UTI and can contribute to urinary tract infections or sepsis. As such, they should be viewed as a last resort when all else has failed or when there is accompanying local skin breakdown.

In terms of pharmacological therapy, anticholinergic or antimuscarinic agents help relax the bladder and increase bladder capacity. These agents are used for incontinence with detrusor overactivity (e.g., urge incontinence). Medications available for urge UI include oxybutynin (Ditropan), tolterodine (Detrol), fesoterodine (Toviaz), solifenacin (Vesicare), darifenacin (Enablex), propiverine (Mictonorm), and trospium (Sanctura). Mirabegron (Myrbetriq) is a relatively newer drug in the class of beta-3 adrenergic agonists which also is used as an alternative to antimuscarinics to treat urge incontinence. A recent systematic review found that mirabegron had similar efficacy to the common antimuscarinics with less cholinergic side effects [9]. Before starting any of these medications, ensure a normal post-void residual (PVR) volume as urinary retention may occur. Systematic reviews of randomized trials have found that antimuscarinics compared with placebo have a modest benefit over placebo in reducing urgency UI. In the largest systematic review to date [10],

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which included 96 randomized trials, fewer than 200 women per 1000 treated with medications achieved continence. Similar efficacy was demonstrated for all antimuscarinic agents (darifenacin [Enablex], fesoterodine [Toviaz], oxybutynin [Ditropan], solifenacin [Vesicare], tolterodine [Detrol], and trospium [Sanctura]). The role of topical estrogen replacement therapy in UI treatment in women remains unclear. That is, there is widespread anecdotal evidence that topical estrogen replacement therapy is effective in treating UI in postmenopausal women, but the literature is contradictory. Vaginal pessary is another nonsurgical treatment often used in elderly women for prolapse. The local pressure effect of these can cause erosions so they should be used with estrogen therapy [11]. In men with overflow incontinence, two classes of medication have been shown to decrease symptoms: alpha-adrenergic antagonists and 5-alpha reductase inhibitors. The alpha-adrenergic antagonists include terazosin (Hytrin), tamsulosin (Flomax), prazosin (Minipress), or doxazosin (Cardura). Patients on alpha-adrenergic antagonists must be monitored for orthostatic hypotension, dizziness, peripheral edema, tachycardia, nasal congestion, impotence, and first-dose syncope. The 5-alpha reductase inhibitors finasteride (Propecia, Proscar) and dutasteride (Avodart) also can be quite helpful.

Nocturnal polyuria also can contribute to incontinence at night and there is some variation in the amount of urine produced at night by age. However, if more than one-third of the daily urine production occurs at night, that is considered to be abnormal. There are many causes of nocturnal polyuria including abnormality of vasopressin secretion (low), secondary to medications (like diuretics and beta-blockers), increased fluid, caffeine, or alcohol intake, third spacing of fluid, and sleep apnea. In the case of third spacing of fluid due to causes such as congestive heart failure and venous stasis, consideration could be made to give diuretics in the late afternoon. For those patients who have abnormal vasopressin secretion, a trial of desmopressin could be considered to attempt to increase to time to first nocturnal void [12]. Surgery can be used for various clinical scenarios of UI. Retropubic suspension and sling can be used for stress incontinence. If overflow incontinence is due to obstruction (e.g., benign prostatic hyperplasia), surgery may be required (e.g., transurethral resection of the prostate).

Falls

Falls are the leading cause of fatal and nonfatal injuries among the elderly in the United States. In 2015 alone, falls cost approximately $50 billion in direct medical costs [13]. The incidence of falls increases with age from 30% to 40% per year in patients over 65 years living in the community to 50% for those over 80. In those over 70 years of age, 41% of falls result in minor injury with 6% resulting in major injury. Five percent of falls in older patients will lead to hospitalization.

All community-dwelling seniors should be screened annually for falls by asking the following question: "In the past year, have you had a fall (including a slip or trip where you lost your balance and ended up on a lower level)?" If the answer is "yes" to more than one slip, trip, or fall, an injurious fall, or balance and mobility problems, conduct a multifactorial falls risk assessment. The reason the assessment is multifactorial is because falls in older adults often are not due to a single cause. A fall history and their circumstances should be completed including date, time of day, location, circumstances (e.g., what the patient was doing at the time of a fall, patient's perception as to the cause, associated symptoms preceding the fall such as chest pain, shortness of breath, palpitations, dizziness), and circumstances after the fall (e.g., loss of consciousness, injuries, post-fall interventions, severity of the fall, duration of any changes in activities of daily living [ADL]/mobility status, and in the patient's confidence in walking and/or fear of falling). Some find the "SPLATT" [14] mnemonic useful:

- *S*ymptoms
- *P*revious falls
- *L*ocation
- *A*ctivity
- *T*ime
- *T*rauma

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History also should include medications currently taken, the use of alcohol, the presence of acute and chronic medical conditions, function (e.g., assessment of basic and instrumental activities of daily living-IADLs), mobility, and lower urinary tract symptoms (LUTS) (e.g., urinary urgency, frequency, nocturia, and urge incontinence). Certain LUTS (i.e., urge incontinence, mixed incontinence, overactive bladder, nocturia) increase the risk of falls among older individuals by up to twofold. A comprehensive medication review by a physician, nurse practitioner, or pharmacist should be conducted on all elderly patients who have had multiple falls or an injurious fall. All medications, their doses, and frequency of use should be reviewed at least annually [15]. The 2019 Updated American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults noted that the following medications may exacerbate a history of falls or fractures: antiepileptics, antipsychotics, benzodiazepines, nonbenzodiazepine hypnotics, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and opioids [16]. Moderate risk medications that are more weakly associated with falls include anticonvulsants and cardiovascular agents (e.g., antihypertensives, antiarrhythmic medications, beta-blockers, peripheral vasodilators, and nitrates).

The physical examination should cover the following: A neurologic examination including mental status, lower extremity strength (e.g., Can the patient stand from sitting without using their arms?), vision, vestibular function (e.g., detection of movement-provoked dizziness by first shaking the head side to side and then nodding it up and down, a head impulse test if trained to do it and there are no contraindications such as severe cervical arthritis), lower extremity sensation and reflexes, a search for extrapyramidal signs (e.g., tremor, rigidity, akinesia, and postural instability), and coordination. A musculoskeletal examination focusing on the lower extremities (e.g., joints, range of motion, pain, deformities) and feet/footwear (e.g., foot problems such as plantar fasciitis, hallux valgus, bunions, ingrown toenails, onychogryphosis, and multiple foot problems) are associated with an increased risk of falling. In-home falls have been associated with being barefoot or wearing socks without shoes and/or proper-gripped slippers. A cardiovascular examination should include assessment of heart rate and rhythm, orthostatic pulse, and postural blood pressure (supine and standing). A blood pressure drop of 20 mm Hg or 10 mm Hg is considered clinically significant. Regular eye assessments should be encouraged. Assessment for osteoporosis including asking about prior osteoporotic fractures and any past bone mineral density tests should be done. Inquiry about historical heights and measurement of current height also should be done, with a historical height loss of greater than 6 cm suggesting the presence of vertebral fractures. Measurement of the occiput-to-wall distance should be done, with an occiput-to-wall distance of greater than 5 cm indicative of the presence of kyphosis which may be the result of vertebral fractures. An assessment of rib to pelvis distance should be conducted, with two or less fingerbreadths suggestive of the presence of vertebral fractures [17]. Screening tools such as the Timed Up and Go test [18] can be used to predict the risk of falls. Once an older adult has been identified as having decreased lower extremity strength or impaired balance, based on either simple observation or outcomes from fall risk screening tools, referral to a physiotherapist is recommended for a detailed assessment of the physical factors which may be contributing to fall risk.

There are a number of interventions that can reduce the risk of falls in seniors. In elderly patients with impaired vision, interventions include good lighting, use of contrasting paints or carpet to mark the edge of stairs, and advising on the avoidance of wearing bifocals while walking. Treatment of orthostatic hypotension also is an important consideration with treatment dependent on the most likely cause. History taking should focus on the type of dizziness: Vertigo (a false sense of motion often described as a spinning or whirling sensation), disequilibrium (feeling off-balance or wobbly), or presyncope (a feeling of lightheadedness or feelings of blacking out or fainting). For many elderly patients, categorization of dizziness may be difficult in

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that the patient may have multiple types of dizziness. Common causes of vertigo include benign paroxysmal positional vertigo (BPPV), vestibular neuritis, and Meniere's disease. Orthostatic (postural) hypotension is a possible cause of presyncope. There are multiple possible causes of disequilibrium such as stroke, Parkinson's disease, sensory impairments (e.g., peripheral neuropathy), and adverse effects of medications. Management is directed at the cause. In general, elderly individuals should wear shoes with low heels and firm slip-resistant soles both inside and outside the home.

Treatment of osteoporosis also is important. Ensuring adequate intake of calcium through dietary sources and supplementation with vitamin D 800–2000 IU is recommended. Depending on the severity, medication treatment of osteoporosis with bisphosphonates, RANK ligand inhibitor (denosumab), selective estrogen receptor modulators (raloxifene), parathyroid hormone (teriparatide), or hormone replacement therapy may be warranted. Hip protectors (devices that absorb and shunt the energy of the impact of a fall away from the greater trochanter) have a role in preventing hip fractures among those at high risk of falls if the patient is willing to wear them. High-risk older adults in long-term care facilities may benefit from their use, but their utility in preventing hip fractures among the elderly in the community is not proven [19]. Physiotherapy is recommended for older patients with lower extremity weakness and/or impaired gait and balance. For the elderly patient living alone or left alone for long periods, an emergency response system should be considered. A home safety checklist for assessment of environmental risks can be used by elderly patients and/or their families. Referral to an occupational therapist may be made for high-risk elderly patients [20].

In summary, the most efficacious interventions reported for elderly patients who are at high risk for falls include adaptation or modification of the home environment, discontinuing or tapering psychoactive medications, discontinuing or tapering of other medications (e.g., anticholinergics, benzodiazepines, hypnotic sedatives, and antihypertensives), minimizing postural hypotension, management of foot problems and footwear, and exercise, especially balance, strength, and gait training. See Fig. 1 for an algorithm in the prevention of falls in older persons living in the community from the American Geriatrics Society and British Geriatrics Society [21].

Orthostatic Hypotension

Orthostatic hypotension (OH) is defined as a "sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing or head-up tilt to at least 60° on a tilt table" ([22], p. 46). It is estimated to be present in up to 70% of institutionalized elderly and 6% of community-dwelling elders [22]. Measuring the blood pressure after sitting (not lying) will miss some cases of OH. However, there is some controversy regarding how long to wait after standing before measuring blood pressure (BP). Generally, the standing BP is measured at 1 min (for screening purposes, a single 1-min reading is usually sufficient) and 3 min after standing.

The recommended approach is to diagnose the underlying cause of OH and manage it. An important step is to review medications and discontinue or reduce medications that may be contributing to the problem. Ensure adequate fluid intake. Modify salt restriction where appropriate. Use compensatory strategies (e.g., elevate head of the bed, rise slowly, dorsiflex feet before getting up). Use pressure gradient stockings (preferably thigh high) where appropriate. Consider pharmacological therapy (e.g., fludrocortisone [Florinef], midodrine [Orvaten, ProAmatine], pyridostigmine [Mestinon]) if the above strategies are unsuccessful and there are no contraindications. See the Finding Balance website for resources targeted for both older adults and medical practitioners (https://findingbalancealberta.ca/).

Polypharmacy

There are varied definitions of polypharmacy, from using inappropriate prescriptions to using five or more prescriptions. Depending on the

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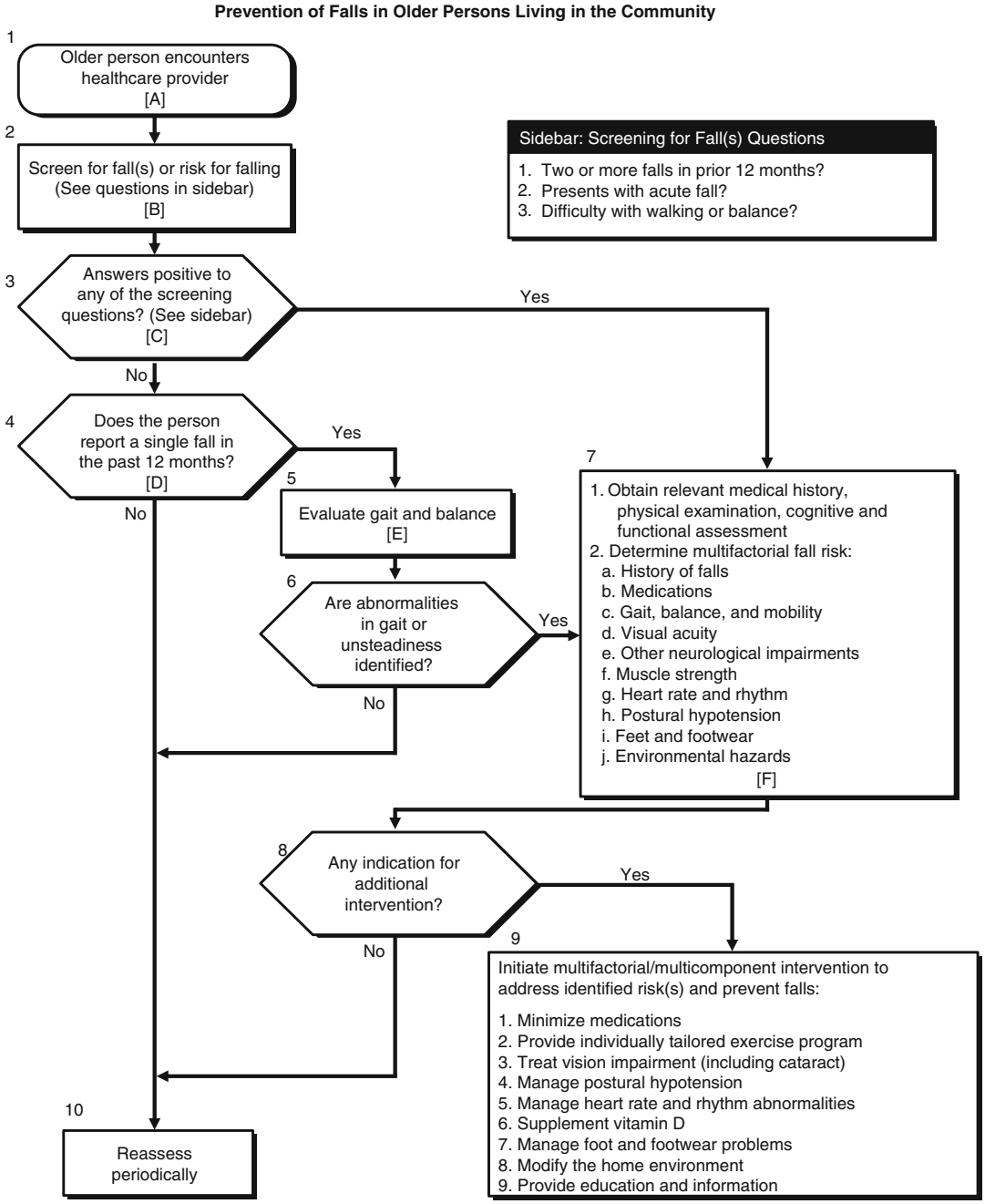


Fig. 1 Prevention of falls in older persons living in the community. This is an algorithm for screening and assessment of falls in older persons, developed by the Panel on Prevention of Falls in Older Persons of the American Geriatrics Society and British Geriatrics Society (Originally published in 2012; with kind permission of © John Wiley and Sons 2011. All Rights Reserved)

definition, the incidence of polypharmacy varies from 5% to 78%. It is estimated that the worldwide costs of polypharmacy is $18 billion US [23]. Inappropriate drug prescribing may lead to avoidable adverse drug events (ADEs). ADEs should be considered to be the cause for any new

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symptom in an older adult until proven otherwise. ADEs occur two to three times as frequently in older persons. Patients taking fewer than three drugs have a 1–2% risk of ADEs whereas those taking more than six drugs have a 13% risk of ADEs. Thirty percent of admissions to hospital are because of adverse drug events. ADEs increase hospital length of stay, costs, and mortality. The annual costs of drug-related morbidity in the USA are estimated to be $528 billion in 2016 [24]. Drug-related hospitalizations cause 2.4–6.5% of all medical admissions in the United States in the general population. ADEs are increased in the elderly due to age-related changes in pharmacokinetics and pharmacodynamics, increased comorbidities, polypharmacy, and nonadherence. Drug trials frequently exclude older adults. As a result, approved drug doses may not be appropriate for the elderly population.

An example of prescribing guidelines for the elderly is the Beers criteria. The American Geriatric Society is the steward of the Beers criteria and produces updates on a 3-year cycle. Medications or classes are identified and divided into three categories: potentially inappropriate medications or classes to avoid, medications to avoid with certain diseases/syndromes, and medications to be used with caution in older adults [16]. Another clinically useful prescriber guideline for older patients is the Screening Tool of Older Persons' Prescriptions (STOPP) criteria [25].

Drug categories to avoid in the elderly, regardless of the consensus criteria used, include the following [26]:

1. Anticholinergics (e.g., tertiary tricyclic antidepressants, gastrointestinal antispasmodics, antimuscarinics, antipsychotics, first-generation antihistamines).
2. Sedatives/hypnotics (e.g., barbiturates, long- and short-acting benzodiazepines) should not be prescribed for chronic usage.
3. Anti-inflammatories (avoid chronic usage).
4. Opiate-related analgesics (e.g., pentazocine [Talwin], meperidine [Demerol]).
5. Antiarrhythmics class Ia, Ic, and III (e.g., disopyramide [Norpace] with anticholinergic, negatively inotropic side effects; amiodarone [Cordarone, Nexterone, Pacerone]; digoxin [Lanoxin, Lanoxicaps] > 0.125 mg/day).
6. Cardiovascular (e.g., alpha blockers, alpha agonists, immediate-release nifedipine [Adalat, Afeditab, Nifediac, Nifedical, Procardia], spironolactone [Aldactone] > 25 mg/d with risk of hyperkalemia).
7. Anti-infective (e.g., nitrofurantoin [Furadantin, Macrobid, Macrodantin] with reduced creatinine clearance/pulmonary toxicity).
8. Endocrine (e.g., desiccated thyroid/cardiac, testosterone/cancer risk, sliding scale/hypoglycemia, megestrol [Megace]/deep venous thrombosis, oral hypoglycemic agents/glyburide [DiaBeta, Micronase] with low blood sugars).

Strategies for Appropriate Prescribing

There are several recommended strategies for appropriate prescribing in the elderly [27, 28]. The strategies are as follows:

1. Maintain an up-to-date drug list with indications for all prescriptions, over-the-counter drugs, and herbal supplements.
   a. Consider non-pharmacological options.
   b. Regularly review the need for the drug and stop the drug, if possible.

Medication reconciliation is crucial for transitions of care. It is a process that identifies medication discrepancies, informs prescribing decisions, and prevents medication errors. The process has three steps: verification (medication use history, accurate list), clarification (medications and doses are accurate), and reconciliation (identify any discrepancies between what is ordered and the patient list, making changes to orders, documenting changes, communicating updated list to the next provider). This medication reconciliation process decreases medication errors by 70% and ADEs by 15%.

Structured Medication Review (SMR) [29] is a regularly scheduled discussion between a patient and their doctor/pharmacist/nurse to

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review ALL medications to address how each medication is working, how each medication is taken, and patient concerns. A SMR should be done when the patient asks for a review, if they are on >5 meds or have >3 comorbidities, they have received medications from more than one physician, and/or there has been a medication change in the last 12 months.

2. Know the actions, adverse effects, and toxicity profiles of medications prescribed; avoid and be vigilant of high-risk drugs as identified by the 2019 Beers criteria [16].
3. Start new medications at a low dose and titrate up based on tolerability and response; give a time-limited trial for new medications to determine if the medication is working ("start low and go slow"). Remember to discontinue trialed medications if they prove not to be beneficial.
4. Prioritize medication prescribing – consider the patient's life expectancy/prognosis/quality of life and time to benefit, and modify treatment for the elderly according to life expectancy [30].
5. Avoid using one drug to treat the side effects of another (e.g., prescribing cascade). Consider adverse drug effects as a potential cause for any new symptom.
6. Attempt to use a single drug to treat two of more conditions (e.g., mirtazapine [Remeron] for depression and weight loss in the elderly).
7. Avoid using multiple drugs from the same class or with similar actions.
8. Educate the patient/caregiver about each medication.
9. Know the patient's cognitive function, health literacy, access to care, and financial status/cultural factors/preferences.
10. Provide written information and engage in medication reconciliation ("teach me back" strategy).
11. Arrange a home visit to review medications with a transitional team member if needed.
12. Educate prescribers/MD.
13. Maintain the simplest medication regimen regarding number of medications, routes, and frequency of administration (If possible, once or twice daily dosing is best).
14. Communicate with other prescribers (teamwork between physicians and pharmacists leads to best outcomes); encourage one prescriber to be responsible primarily for monitoring of prescription information to be clearly communicated in a timely manner.
15. Use systems that support optimal prescribing behavior.
    a. Drug utilization reviews.
    b. Automated drug alerts providing information on potential drug interactions or dose problems.
    c. Smartphone reference guides for drug–drug interaction tools.
    d. Pharmacist-led interventions for medication review.
    e. Pharmacist-led interventions and multidisciplinary care (e.g., involving a geriatrician) have been found to be effective in improving appropriate prescribing.

Underutilization (Underprescribing)

Underprescribing of medications also is a significant issue in the older adult population. One study defined underuse of a medication as "the omission of a drug when there is a clear indication and no contraindication" [33, p1096]. It has been found that up to 50% of older adults in a long-term care facility had not been prescribed some recommended therapy [32]. Part of the problem related to underprescribing in the older adult population is due to published guidelines on treatment and management of medical conditions. The vast majority of, if not all, guidelines on drug prescribing are directed at single disease entities while older adults have multiple comorbidities and sometimes one treatment guideline will contradict another. Pain and osteoporosis are two commonly undertreated problems in the elderly. Careful review of the comorbidities and a history of the older adult are necessary to uncover any medications that are omitted but could provide health benefit.

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Pain Management

Pain management is an important issue in the elderly in that pain impacts function and quality of life. Chronic pain is reported by 20–50% of patients in primary care [33]. Assessment of pain in the elderly patient can be difficult especially if there is cognitive impairment or dementia. In addition, acute pain syndromes (e.g., myocardial infarction, acute abdomen) may present atypically in the frail elderly.

WHO Analgesic Ladder

Pharmacologic approaches are the cornerstone of treatment of acute and chronic pain. The World Health Organization (WHO) analgesic ladder was designed to guide treatment of cancer related pain and organizes drug therapy into three steps: (1) nonopioid drugs (aspirin, acetaminophen [Tylenol], nonsteroidal anti-inflammatory drugs [NSAIDs], COX-2 inhibitors), (2) low-dose opioids, and (3) higher-dose opioids [34]. This ladder was widely disseminated and built a standard of practice around pain control not just for cancer patients but also for patient with acute or chronic pain. The recommendation is for treatment to begin with nonopioids, with opioid drugs added as necessary. It is important to realize that when acetaminophen-opioid combinations are used (e.g., acetaminophen with codeine [Tylenol no. 3] or acetaminophen with oxycodone [Percocet]), patients should receive no more than 4 g of acetaminophen per day. NSAIDs and aspirin should be avoided in the elderly if possible due to frequent side effects. When possible, choose oral medications over other more invasive modes of delivery. When pain is localized to specific joints, consider topical NSAIDs as an alternative to systemic NSAIDS. Patients, including the elderly, who have pain most of the day, should receive their drugs (e.g., acetaminophen) regularly and not on an "as needed" basis.

Opioids

The decision to start opioids may be considered for noncancer pain in those with moderate to severe chronic pain that is adversely affecting function and quality of life. The decision to use opioids needs careful consideration. Patients should be stabilized on short-acting opioids before switching to equianalgesic doses of long-acting opioids. Opioid side effects include nausea and vomiting, constipation, pruritus, and CNS effects. A bowel routine should be initiated in all patients taking opioids, with an osmotic laxative such as polyethylene glycol the recommended first-line treatment. For those experiencing sedation, a dose reduction of 25% or opioid rotation may help. An opioid equianalgesic table should be used (see Table 1). In rotating to an opioid other than methadone (Dolophine) or fentanyl (Sublimaze), the equianalgesic dose should be reduced by 25–50%, for methadone 75–90%, and for fentanyl equal dose. As of July 2012, the US Drug and Food Administration introduced a Risk Evaluation and Mitigation Strategy (REMS) for all extended-release hydromorphone (Dilaudid), morphine (Avinza, Kadian, Oramorph, Roxanol), oxycodone (Oxecta, Oxyfast, Roxicodone), oxymorphone (Opana), tapentadol (Nucynta), fentanyl (Sublimaze), and methadone (Dolophine) The REMS involves provider training, patient counseling, and distribution of a medication guide for patients with each dispensing. For more information, see the REMS website: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

Table 1 Opioid equianalgesic table [35]

Drug	Intramuscular dose (mg)	Oral dose (mg)
Morphine (Avinza, Kadian, Oramorph, Roxanol)	10	30
Hydromorphone (Dilaudid)	1.5	7.5
Codeine	130	200
Oxycodone (Oxecta, Oxyfast, Roxicodone)	15	20
Oxymorphone (Opana)	1	15
Methadone (Dolophine)	10	20

Neuropathic Agents

For neuropathic pain, gabapentin (Gralise, Neurontin), pregabalin (Lyrica), or tricyclic antidepressants (TCAs) should be considered as first-

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line treatment. Serotonin-norepinephrine uptake inhibitors (SNRIs) should be considered first or second line. Gabapentin (Gralise, Neurontin) is effective for postherpetic neuralgia and diabetic neuropathy. The drug is started at a low dose and slowly titrated up to effect. Pregabalin (Lyrica) may achieve faster pain control as less time is needed to titrate to a full dose. Other anticonvulsants including topiramate (Topamax), lamotrigine (Lamictal), levetiracetam (Keppra), phenytoin (Dilantin, Phenytek), sodium valproate (Depakote), zonisamide (Zonegran), tiagabine (Gabitril), and clonazepam (Klonopin) have been considered for neuropathic pain treatment, but the research shows there is poor evidence of benefit. An exception would be carbamazepine (Carbatrol, Equetro, Tegretol) for trigeminal neuralgia. Tricyclic antidepressants (TCAs) (e.g., amitriptyline [Elavil], nortriptyline [Pamelor]) may be used for neuropathic pain though their anticholinergic side effects must be considered. Venlafaxine (Effexor) has evidence for use in diabetic neuropathy and polyneuropathies, but not for postherpetic neuralgia. Duloxetine (Cymbalta) has evidence of effectiveness in diabetic neuropathy, fibromyalgia, low back pain, and osteoarthritis.

Since the experience of pain comprises both physical and psychological components, it has been shown that combination therapies are more effective than single therapies [36]. Other adjunctive therapies to be considered in a multifaceted approach are behavioral medicine (e.g., cognitive behavioral therapy, biofeedback, relaxation therapy, and psychotherapy), exercise, acupuncture, physical and occupational therapy, chiropractic, ultrasound, and electrical neuromodulation (e.g., transcutaneous electrical nerve stimulation, spinal cord stimulation), heat/cold, nerve blocks, Botox, and steroid injections.

Nutrition

Nutrition is of vital importance to patients of all ages. It can be particularly important for the elderly as they require fewer calories, but not fewer nutrients, to maintain their weight and health. Approximately 15% of older outpatients and more than 50% of older inpatients are malnourished, with up to 71% of elderly patients at nutritional risk. Dehydration is common among the elderly. This is partly because the sense of thirst diminishes with age. However, there are a variety of other factors contributing to dehydration in the senior population, including voluntary limitation of oral intake due to urinary urgency or frequency or limited access to hydration due to impaired mobility or cognition.

Weight loss in older adults is a concern. Weight loss is usually a combination of inadequate dietary intake, decreased appetite, muscle atrophy, and inflammatory effects of disease. Malignancy is the second most common cause of weight loss in the senior population (16%), with depression being the commonest cause (18%). Physiological factors include a decrease in the acuity of taste and smell with aging, which lessens the enjoyment of eating.

Inadequate dietary intake can include social factors such as poverty, isolation, and difficulty obtaining groceries. Medical factors include poor dentition or poorly fitting dentures which may lead to chewing difficulties. Swallowing disorders are more common in older persons and gastrointestinal motility declines with age. Other risk factors for malnutrition include certain medications (e.g., opioids and diuretics) and illnesses (e.g., dementia). Conditions such as pressure ulcers, chronic infections, malabsorption, malignancy, endocrine disorders, end-organ disease (e.g., congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease, hepatic failure), rheumatological disorders, and alcoholism can increase metabolic demands and result in malnutrition. “MEALS ON WHEELS” is a useful mnemonic for the causes of weight loss in the older adult [37]:

- ***M***edications (e.g., digoxin, theophylline, serotonin reuptake inhibitors, antibiotics)
- ***E***motional (e.g., depression, anxiety)
- ***A***lcoholism, elder abuse
- ***L***ate-life paranoia or bereavement
- ***S***wallowing problems
- ***O***ral factors (tooth loss, xerostomia)

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- ***N***osocomial infections (e.g., tuberculosis, pneumonia)
- ***W***andering and other dementia-related factors
- ***H***yperthyroidism, *h*ypercalcemia, *h*ypoadrenalism
- ***E***nteral problems (e.g., esophageal stricture, gluten enteropathy)
- ***E***ating problems
- ***L***ow-salt, *l*ow-cholesterol, and other therapeutic diets
- ***S***ocial isolation, *s*tones (chronic cholecystitis)

Weight loss is of concern in seniors given its associated mortality in this population. Clinically significant weight loss can be as low as 5% over 3 years. If there is 2% or greater decrease of body weight in 1 month, 5% or greater decrease in 3 months, or 10% or greater in 6 months, this should prompt clinical investigation and workup [37]. There are many screening tools that can be used to assess for malnutrition in the elderly patient. One simple test in the highest quartile for sensitivity (>83%) and specificity (>90%) is the Malnutrition Screening Tool (MST). It asks two short questions: "Have you been eating poorly because of decreased appetite?" and "Have you lost weight recently without trying?" Older adults are less able to adapt to underfeeding, experience less frequent hunger, and are less likely to regain lost weight. This results in chronic, persistent weight changes.

Decreased appetite (anorexia) in the elderly is related to the physiologic factors identified above. Cachexia is a more complex metabolic syndrome related to illnesses that result in loss of muscle with or without fat mass. The illnesses could include cancer, end-stage renal disease, chronic pulmonary disease, congestive heart failure, and/or AIDS. Cachexia is different than starvation, sarcopenia, psychiatric, gastrointestinal, or endocrinological causes of weight loss. With cachexia, there is inflammation and catabolism, often making cachexia resistant to intervention. Sarcopenia is loss of muscle mass, strength, and function that is unrelated to underlying illness. Sarcopenia is present in over 50% of adults 80 years of age and older. It is caused by endocrine changes (e.g., decreased testosterone and estrogen), cytokine changes, decreased physical activity, chronic disease, inflammation, insulin resistance, and nutritional deficiencies (particularly low protein intake).

Nutritional Assessment

Nutritional assessment is important in the senior population. Weight loss can be identified via serial weight measurements. A dietary referral can be made to get a more formal dietary intake assessment. A complete history (including any new medications, diagnoses, or social issues) and physical examination are recommended on a regular basis. Anthropometric measures such as weight, height, body mass index (BMI), and skinfold thickness can be helpful for the initial assessment. Laboratory tests, including a complete blood count (CBC), electrolytes, creatinine, glucose, thyroid-stimulating hormone (TSH), serum albumin, liver function studies (LFTs), and cholesterol levels, may be obtained. Transferrin and prealbumin levels are more sensitive measures of short-term undernutrition. Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) should be done if cachexia is suspected. Chest/abdominal X-rays and abdominal ultrasound may be considered. The strongest predictors of malignancy as a cause for the weight loss are age >80 years; white blood cell count >12,000/mm ^{3}; albumin <3.5 g/dl; alkaline phosphatase >300 IU/L; and lactate dehydrogenase >500 IU/L. In patients with significant ongoing weight loss, a CT chest/abdomen/pelvis should be considered, bearing in mind comorbidities and frailty status. If early satiety is present, gastroscopy should be considered. Referral to a dietitian for assessment and intervention is recommended when the body mass index (BMI) is less than 22 for those patients age 65 years and older and if there is an unplanned weight loss of >2% in 1 month or >10% in 6 months.

Other indicators that place senior patients at nutritional risk and require monitoring or community services include poor appetite; changes in dental health or difficulty in biting and/or chewing; difficulty accessing groceries or making meals due to access, finances, or mental illness; or

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concerns with meal patterns including routine skipping of meals or lack of variety in food intake.

Treatment of Nutritional Deficiencies

An important step in addressing nutritional deficiencies in seniors is identification and treatment of the cause of those deficiencies. Consider removing any dietary restrictions (e.g., restrictions for those on a cardiac diet or diabetic diet). Inquire if shopping and meal preparation are being accommodated and if assistance with feeding is required. Ensure that recommended foods fit the patients' ethnic or religious preferences. Increase nutrient density of foods. Protein content can be increased with milk, whey powder, egg whites, or tofu. Fat content can be increased by adding olive oil to sauces, vegetables, grain, or pasta. If these fail to increase weight, snacks should be added. Consider liquid nutritional supplementation. These have been shown to increase weight (more so in patients at home or in long-term care) and to improve mortality, except in those living at home. When there is refusal or inability to swallow, enteral tube feeding with a small-bore nasogastric tube (NGT) or percutaneous enteral gastrostomy (PEG)/jejunostomy (PEJ) tube may be considered. The decision on which of these methods to use depends on patient preference, suspected length of time the feedings will be necessary, and patient tolerance. Feeding can occur in a continuous fashion or with intermittent bolus feeds. There is an increased risk of aspiration with both NGT and PEG feeding. Total parenteral nutrition (TPN) is indicated in the elderly patient when there is an inability to use the gut to meet nutritional needs. Complications associated with TPN are more likely to occur in the elderly population. In patients with advanced dementia, there is limited evidence for benefit with enteral feeding.

Appetite stimulants may play a role in addressing nutritional deficiencies. In seniors with cancer, megestrol acetate and steroids have been used. In older patients treated with megestrol acetate (Megace), observation for complications such as congestive heart failure and deep vein thrombosis is needed. Dronabinol (Marinol) has been shown to increase appetite in patients with AIDS. Mirtazapine (Remeron) could be considered to increase appetite and induce weight gain in patients with depression.

Pressure Ulcers

Pressure ulcers are defined as ischemic soft-tissue injuries that result from pressure over bony prominences (e.g., sacrum, calcaneus, ischium). Pressure ulcers are a significant problem for older adults with comorbidities, as well as for those in long-term care and critically ill patients. Patients with spinal cord injuries or stroke are at particular risk for the development of pressure ulcers. Pressure ulcers are associated with pain, reduced quality of life, and increases in morbidity and length of stay in hospital. The best treatment for pressure sores is prevention, but even under the best conditions, prevention is not always possible.

Assessment and Staging of Pressure Ulcers

Pressure ulcers should be assessed for stage, size, exudates, necrotic tissue, sinus tracts, and granulation. The National Pressure Ulcer Advisory Panel is the most common system of staging ulcers, with staging as follows:

- Stage 1 – Localized, non-blanching erythema.
- Stage 2 – Partial thickness loss of dermis.
- Stage 3 – Full-thickness skin loss and fat may be visible.
- Stage 4 – Full-thickness skin and tissue loss with exposed bone, tendon, or muscle.
- Unstageable – Obscured full-thickness skin and tissue loss.

Treatment of Pressure Ulcers

Historically, the standard of care for prevention of pressure ulcers has been focused on positioning and regular turning of bed or chair-bound seniors

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at least every 2 h. However, the evidence for this practice is quite poor with the few randomized controlled trials being underpowered and at high risk of bias [38]. One study has shown no difference in the development of pressure ulcers in a population of bed-bound seniors post hip fracture with 2 h repositioning versus patient turned less often. More studies are required to determine the optimal frequency of repositioning. Once a pressure ulcer has developed, positioning and support surfaces need to be reviewed and changed as needed. Wound care with debridement of any necrotic tissue is necessary. Negative-pressure wound therapy may be considered. The wound should be monitored on a daily basis including the ulcer itself, the dressing, and the area around the ulcer. Monitoring for the presence of pain and complications such as infection is needed. Older adults with pressure ulcers commonly are in a catabolic state and need protein and calorie optimization. While vitamin C and zinc are commonly prescribed to promote wound healing, there has been no conclusive research supporting this treatment. Pressure-relieving support surfaces also are utilized to promote wound healing. These include non-powered surfaces like foam; overlays of foam, air, or water; and powered mattresses. There is moderate quality evidence for ulcer prevention through the use of alternative foam mattresses but low-quality evidence for the use of alternating pressure mattress, sheepskin, gel pads in surgery, and suspension beds in the intensive care unit (ICU) [39]. Attention to pain control and comfort is important.

Dressings

Stage 1 pressure ulcers can be dressed with transparent films for protection. Stage 2 pressure ulcers require an occlusive or semipermeable dressing to maintain a moist environment. The treatment of Stage 3 and 4 pressure ulcers depends on the amount of exudate, desiccation, necrotic tissue, or infection. If there is heavy exudate, an absorptive dressing (e.g., alginates, foams, and hydrofibers) is required. For desiccated wounds, saline-moistened gauze, transparent films, hydrocolloids, and hydrogels are needed. Debridement of all necrotic tissue is important. This can be achieved via sharp debridement with scalpel or scissors, mechanical via wet-to-dry dressings, enzymatic using collagenase/fibrinolysin or deoxyribonuclease, or autolytic via semiocclusive (transparent) or occlusive dressings (hydrocolloids or hydrogels). Most pressure ulcers will heal with treatment. Using the above measures, over 70% of Stage 2, 50% of Stage 3, and 30% of Stage 4 pressure ulcers are healed at 6 months [40]. However, surgery is sometimes required using skin grafts, skin flaps, musculocutaneous flaps, and free flaps.

Transitions of Care

As people grow older, they often struggle to achieve a balance between maintaining independence and accepting help. Most older adults would like to live at home for as long as possible. However, caregivers may find that they are overwhelmed and exhausted with providing care to an older family member. As such, it also is important that caregivers receive support to ensure they can continue to provide care while also maintaining their own well-being.

Determining Support Needs

Elderly patients living at home often have challenges in day-to-day routines including personal care such as bathing or more difficult tasks like transportation, grocery shopping, managing money, and/or house maintenance. The elderly patient and family should be advised to seek out supports and resources before they are needed or before the situation becomes urgent. Information about supports and resources may be in a variety of formats – online, telephone, and referral-based as well as in- person. The availability of some supports and resources may depend on where the older person lives. Aspects that elderly patients should consider in determining needs:

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1. Preferences: What is important to me? What do I value?
2. Support network: What help can my family and friends provide?
3. Eligibility: What services am I eligible for?
4. Availability: What services are available in my community?
5. Finances: What can I afford?
6. Timing: How much time do I have to make a decision?

Community Supports

Community supports that allow patients to maximize their potential and function in their home environment for as long as possible are available in many communities. Community supports occur in many settings, such as faith-based programs, community-driven programs (e.g., leagues or groups), local programs (e.g., Seniors' Associations, Meals on Wheels), advocacy groups, and through national programs (e.g., Alzheimer Society). Some community supports may include services that are available with or without cost (e.g., equipment, homemaking services, transportation).

Healthcare Resources

Healthcare resources are typically more formal and structured than community supports. They usually require a referral and may include a cost. These types of resources include the following: home care, in-home professional health services, day programs, day hospitals, mental health services, respite services, rehabilitation services, equipment assessments, and publicly funded housing supports.

Levels of Care

When older adults can no longer manage to live in their own homes, various levels of care are available. Levels of care often are based on the type and amount of care needed. It is never too early to discuss alternative types of housing and to begin planning for the future. The Continuing Care system provides various types and levels of care for older adults that support their independence and quality of life. In Canada, for example, there are three settings in which the Continuing Care system provides accommodation, healthcare, and personal services. These settings are Home Living, Supportive Living, and Facility Living. Careful assessment is important because a less restrictive environment may be a better solution and because patients and families often are not aware of these options. Family physicians should evaluate patients thoroughly, focusing on their functional abilities and identifying what areas they require help with. A mental status examination is important, as patients may appear relatively intact on casual questioning but actually suffer from severe cognitive impairment.

Home Living

Home living services provide home-based care for the elderly who live in their own home, apartment, or another independent setting. Home living can provide in-home professional support services such as nursing and rehabilitation, personal support services, and equipment. Examples of personal support services include medication assistance, bathing, or grooming assistance.

Supportive Living

Supportive living combines accommodation services with other supports and care. Supportive living settings vary by size and types of services provided. It can include meals, housekeeping, and social activities. Residents pay a fee to cover the cost of accommodation and needed services. Residents also can receive professional and personal support services through home living (home care). These support services can be provided by private for-profit, private nonprofit, or public operators. Examples include seniors' lodges, group/personal care homes, private supportive living, and designated supportive living. Designated supportive living settings have additional health and personal care services which are funded publicly.

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Facility Living

Facility living includes long-term care facilities such as nursing homes and auxiliary hospitals. Care and accommodation services are provided for people with complex health needs who are unable to remain at home or in a supportive living setting. In facility living, residents pay an accommodation fee to cover the costs of providing accommodations and services such as meals, housekeeping, and building maintenance. Health services in facility living are publicly funded.

Older Drivers

On a per capita basis, elderly drivers' fatal crash rates begin to increase at 70 years of age. Factors contributing to the higher crash rates of elderly drivers include impairments in functional abilities to drive (e.g., sensory, motor, cognitive) as a result of age-related changes in driving skills, the presence of one or more medical conditions, and/or the drugs used to treat those conditions. Evidence implicates the role of medical conditions more so than age-related changes [41]. In particular, drivers with cardiovascular disease, pulmonary disease, diabetes, psychiatric disorders, visual disturbances, musculoskeletal disorders, neurological conditions, and cognitive impairment were at greatest risk for at-fault crashes in a large population-based study [41]. The higher crash and fatality rates of older drivers have prompted calls for tighter legislation for older drivers, particularly at the time of license renewal. It also has resulted in the need for a test or tests to evaluate the driving competence of elderly drivers.

Evaluating Older Drivers

The medical community often is called upon to provide an assessment of "fitness to drive." To assist with this process, a number of medical associations have developed medical fitness to drive guidelines (e.g., the Canadian Medical Association's Determining Medical Fitness to Operate Motor Vehicles: A Guide for Physician – 9.1 Edition [42] and The American Medical Association Physician's Guide to Assessing and Counseling Older Drivers [43]). Medical history should cover history of coronary artery disease, stroke, movement disorders, seizures, diabetes, sleep disorders, arthritis, and the presence of illness such as dementia. Prescription and over-the-counter medication use should be documented. Research has shown that benzodiazepines increase motor vehicular crashes (MVCs) by fivefold, antidepressants 1.8 times, and opioids 1.5 times. Alcohol and other substance use should be ascertained in any assessment of fitness to drive.

Driving history should cover how often the senior drives, MVCs or traffic violations in the last year, and getting lost while driving. If a caregiver is present, they can be asked if they have accompanied the patient as a passenger recently and whether they have any concerns about the patient's driving.

A physical examination should be done to look at mobility (gait and balance), function, vision, and cognition. The neck, shoulders, and wrists should be examined for range of movement. Common tests for assessment of "cognitive fitness to drive" include the Mini-Mental State Exam (MMSE), Trails A and B, and clock drawing. However, none of these tests is very predictive although the American Academy of Neurology suggests an MMSE score of $\leq$24 identifies patients at risk of unsafe driving. The SIMARD MD is a paper and pencil test developed to assist healthcare professionals in identifying cognitively impaired drivers with good predictive properties on identifying those failing and passing an on-road test and those who are indeterminate and in need of further assessment [44]. Many pen and paper cognitive tests rely on proficiency of the English language and may be a significant disadvantage to those for whom English is not their first language. One of the advantages of the SIMARD MD is that this test is available in nine languages (Arabic, Chinese, English, French, Hindi, Punjabi, Spanish, Tagalog, and Vietnamese), with the tests available at no cost. When assessing patients from diverse backgrounds, using cognitive screening tools available in other languages

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or concentration on functional testing should be considered.

Mandatory reporting of moderate to severe dementia is required in some US states and 7 of the 10 provinces and all 3 territories in Canada. On-road testing may pick up more unsafe drivers than cognitive testing. However, unless they are specifically adapted for drivers with cognitive impairment, regular road tests (e.g., on-road assessments designed to test "basic" driving skills) may fail to detect safety issues in this population of drivers due to overlearned skills [45].

The primary care physician is an essential partner in assessing driving competency. While many families have concerns, they often do not feel able to discuss it with their family member. In the interests of maintaining the family physician-patient relationship and if the patient has already been referred to geriatrics for cognitive assessment, assessment of and discussions related to fitness to drive may be done by the specialist. If drivers have a physical disability, vehicle adaptations could be made to address this disability (e.g., peripheral neuropathy [foot drop]). In addition, alternate transportation services for seniors (e.g., modes of transportation that exist outside of public transportation programs and include both for-profit and not-for-profit services delivered via private vehicles, buses, handibuses, handivans, minivans) are available in many urban and rural, and to a lesser extent in remote areas. These alternate transportation services enable many older adults to meeting their medical, essential, and social/recreational needs, as well as reducing the risk of social isolation in older adults who voluntarily or involuntarily stop driving [46].

Breaking bad news and driving cessation support programs have been developed and can be useful for patients and their families [47].

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Alzheimer Disease and Other Dementias

24

Richard M. Whalen

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General Principles

Dementia is a common problem seen by family physicians. There is no disease-modifying agent currently available for treating progressive dementias such as Alzheimer's. Cognitive-enhancing medications can be offered on a trial basis but have very limited benefit. Recent studies support the benefits of vigorous exercise in delaying the onset or slowing the progression of most dementias [1]. Management should focus initially on patient and family education and early discussion of goals of care. Physicians should look to evidence-based guidelines to help provide high-value interventions for the prevention and management of common complications of dementia. These include depression, delirium, agitation, falls, adverse medication effects, and burdensome, distressing interventions near the end of life. Advanced dementia can be devastating for both the patient and family. Support from a trusted family physician during this difficult time can be invaluable.

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Approach to Care: Older adults should undergo routine cognitive screening in venues such as the *Medicare Wellness Visit*. Screening can be done through a number of available tools including the *Mini-Cog* (3-item 5-min recall and clock draw) [2]. If the initial screening is abnormal, a more detailed, quantifiable test such as the *Montreal Cognitive Assessment* (MoCA) or the Mini-Mental Status Exam (MMSE) should be considered. These are more widely accepted as reliable for tracking disease progression and statistical responses to treatment. Evaluation for reversible causes of cognitive impairment should also be done (Table 1). If this is negative, it is highly probable that the patient suffers from one of the common nonreversible dementias. A consultation should be considered if the diagnosis is in doubt.

Definition/Epidemiology

Estimates of dementia prevalence vary widely due to imprecise diagnosis and documentation. Average estimates are about 4% for people aged 55–65, 10% aged 65–75, 20% aged 75–85, 30% aged 85–90, and 40% aged >90. In 2020 there were approximately 5.8 million people in the USA with dementia. This number is expected to increase to 13.8 million by 2050 [4].

The 2013 revision of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5) introduced *neurocognitive disorder* (NCD) to replace the preferred term for dementia. The main rationale was the perceived stigma attached to the diagnosis of dementia, especially in younger persons. It recognizes that the term dementia is still appropriate for the use in settings where it is customary [5].

The diagnostic criteria for dementia are [5]:

1. Cognitive impairment involving at least one of the following domains: memory, language, complex attention, executive function, perceptual (visual-spatial) motor function, and cognitive behavior.
2. This must represent a decline from a prior level of function.

Table 1 Reversible dementia/cognitive impairment

Drugs	Any medication with anticholinergic, sedating, or other CNS effects should be suspect. Renal impairment will magnify side effects. Effects may be additive so polypharmacy should be addressed even if there is not a single "smoking gun" medication. See "Beers List" for further details [3]
Eyes/ears	Lack of sensory input over time will hasten cognitive decline. Severe hearing or visual impairment can lead to an incorrect diagnosis of dementia if a hurried clinician does not adjust their assessment appropriately
Metabolic	Thyroid disease and B_{12} deficiency should be ruled out. Renal function, CBC, and liver function tests are also recommended
ETOH	Alcohol abuse can cause short-term memory impairment and other neurologic deficits. Deficits may improve at least partially with cessation
Normal pressure hydrocephalus	This usually presents with gait instability and possibly urinary incontinence before dementia becomes apparent. The gait is usually wide based with steps close to the floor ("magnetic") and normal arm swing. This differs from a parkinsonian gait with limited arm swing due to bradykinesia and rigidity
Tumor/trauma	Tumors or trauma, including subacute or chronic subdural hematoma, may present with cognitive impairment. There are usually additional neurologic signs
Infections	Testing for *neurosyphilis* is no longer routinely recommended for all dementia patients. It should be considered if presentation is atypical with early neuropsychiatric symptoms or if HIV positive. HIV dementia is common in late-stage disease
Affect/depression	Depression can result in low scores on cognitive tests due to lack of engagement (*Pseudodementia*). Long-standing depression can cause true cognitive impairment due to diminished social and mental stimulation
Sleep apnea	This is now recognized as potentially contributing to cognitive decline, although it is usually a minor factor

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3. Reversible causes of cognitive impairment including delirium have been ruled out.
4. There is loss of independence due to impaired functional status in activities of daily living (ADLs) or independent activities of daily living (IADLs).

If criteria 1–3 are present but independent functioning is preserved, even with the help of compensatory strategies by the patient, the diagnosis is *mild cognitive impairment* (MCI), not dementia. About 30% of people with MCI will progress to dementia within 5 years. MCI can be amnestic (memory impaired) or non-amnestic. The progression to dementia is highest in research settings if patients have amnestic MCI with biomarkers suggestive of Alzheimer's pathology (see below) [6].

DSM-5 has added additional specifications for the likely etiology of the dementia (Table 2).

Table 2 Common dementias and their characteristics

Progressive (neurodegenerative) dementias: The underlying pathology inevitably progresses, although at varying rates. A terminal stage will be reached unless death from another cause supervenes. There is significant overlap among AD, LBD, and VaD	
Alzheimer's disease **(AD)** (65–70%)	Characterized by insidious onset with short-term memory decline as the earliest deficit in most people. Language and visual-spatial changes may be the initial deficit in about 5%. Pathologic changes begin years before clinical features develop. There is overlap with Lewy body dementia (LBD) and vascular dementia (VaD), especially in older age groups
Lewy body dementia **(LBD)** (15–20%)	Characterized by visual hallucinations and spontaneous fluctuations in mental status. REM sleep disorder (vivid dreams physically acted out) may be the earliest sign. Most people will develop parkinsonian features eventually, which may be subtle If cognitive impairment develops after the onset of Parkinson's disease, it is known as **Parkinson's disease with dementia (PDD)**
Frontotemporal dementia **(FTD)** (5%)	Age of onset is generally earlier than AD and LBD, often in the 40s or 50s. There also appears to be a hereditary component more frequently. There are three subgroups. The most common is FTD-behavioral variant (Pick's disease) which affects personality and behavior early in the course when memory may be well preserved. Less common are semantic dementia and primary progressive aphasia which affect speech and language initially
Prion disease (<1%)	Rapidly progressive with changes in behavior, coordination, and vision in most. Caused by communicable proteins in CNS, though most cases arise spontaneously. Dx is by CSF 14-3-3 protein levels. Creutzfeldt-Jakob disease (CJD) is the most common form. Incidence about 1/1 million/yr
Secondary dementias: (may be stabilizable)	
Vascular (VaD) (15–20%), usually a cofactor rather than the primary etiology	Deficits vary depending on location and extent of the stroke(s). More likely to be the primary etiology in the oldest age group (>90) It is important not to confuse expressive aphasia or dysarthria with dementia if nonverbal communication is preserved
Alcohol (<5% as primary factor)	Short-term memory deficits most prominent in chronic overuse. Ataxia also is common. Dementia may partially improve after alcohol cessation
Brain injury from isolated trauma (TBI) or hypoxia (<1%)	Multiple presentations depending on extent or site of brain injury. Cognitive deficits may be subtle if injury or hypoxia was relatively mild. Usually is not progressive
Chronic traumatic encephalopathy (<1%)	Due to repeated trauma such as concussions in athletic injuries. May have changes similar to FTD, with personality changes a prominent early feature and tau proteins on pathologic study. May have insidious onset and progression

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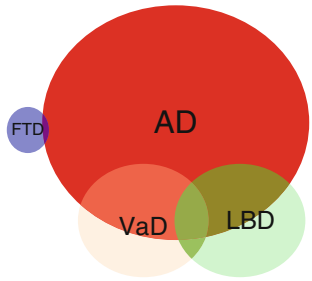


Fig. 1 Prevalence and overlap of common dementias. **Alzheimer's disease (AD) = 65–70%. Lewy body dementia (LBD) = 15–20%. Vascular dementia (VaD) = 15–20%. Frontotemporal dementia (FTD) = 5%**

There is significant overlap of the most common dementia etiologies (Fig. 1).

It is now recognized that Alzheimer's pathology develops years before clinical symptoms of MCI or subsequent dementia. This pathology includes beta-amyloid deposits outside of neurons, tau protein tangles within neurons, and hippocampal shrinking. The National Institutes of Health (NIH) working group on Alzheimer's has therefore proposed the revision of Alzheimer's disease diagnosis and staging. Three stages are identified: preclinical, MCI, and clinical disease [6].

Biomarkers which are usually abnormal in all three stages of AD include *amyloid PET scans*, structural MRI, and CSF proteins. They are now being used in research of therapies designed to impact the pathological processes. Medicare has approved the preauthorized use of *biomarkers* for the evaluation of dementia when the diagnosis is in doubt and it is felt that a precise diagnosis is clinically important. This group would typically include younger patients or those with atypical or rapidly progressive symptoms [7].

Approach to the Patient

History and Physical Examination

A focused history and physical should be performed if cognitive impairment is suspected based on abnormal screening tests or symptoms reported by the patient or family. Key areas are:

History of Present Illness: Time course regarding onset/progression of cognitive change or other symptoms is critical. Insidious onset and slow progression of symptoms are characteristic of AD, LBD, and FTD. A family member is usually needed to provide a reliable report of this. More abrupt onset is of concern for stroke or other secondary or reversible causes of cognitive impairment (see Tables 1 and 2).

Family History: A positive family history of FTD increases the likelihood of FTD as the etiology, especially if behavior/personality changes are presenting symptoms. About 20% of FTD is inherited through an autosomal dominant gene [8]. FH of AD or LBD/PDD confers a more modest increased risk. Age is by far the highest risk factor for these.

Medical History: This should include history of stroke, Parkinson's, depression, syphilis, HIV, *Down's syndrome* (which frequently leads to AD), or other neuropsychiatric disorders.

Medications: A careful medication review will often reveal additive CNS side effects from multiple medications.

Social History: Screening for alcohol abuse is important. Risk factors for cardiovascular disease such as smoking, poor diet, and lack of exercise are also associated with increased risk for MCI and dementia. *Social isolation* increases the risk for dementia.

Speech/Affect/Memory: Fluent speech with socially appropriate, normal affect but impaired short-term memory is suggestive of MCI or early AD. Blunted speech which may be socially inappropriate at times should raise concern for FTD. LBD/PDD may have more blunted speech or more difficult with retrieving long-term memory facts than AD with better short-term memory in early and middle stages. Flat affect or lack of engagement during the assessment may indicate depression (pseudodementia).

Gait/Motor/Sensory: These should be normal in early-middle stage AD. PDD will have clear parkinsonian features as by definition these develop before the dementia. Parkinsonian features usually develop at some point in LBD but may be subtle. *Gait* changes with a

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wide-based, shuffling ("magnetic") gait with good arm swing are suggestive of NPH. The arm swing in Parkinson's is usually diminished due to rigidity or bradykinesia. *Neurosyphilis* signs may include diminished proprioception with high-stepped gait or weakness (tabes dorsalis) or small pupils that don't react (Argyll Robertson pupils). Upward gaze palsy in a patient with parkinsonism is diagnostic of progressive supranuclear palsy, a Parkinson's plus syndrome that usually leads to dementia.

Lab/Imaging

Basic labs to rule out non-neurodegenerative etiologies of cognitive impairment should be done, including CBC, liver and renal function, TSH, and B12. A onetime head CT/MRI can be considered, especially if there are early changes in behavior, speech, vision, or motor functions which could suggest a non--Alzheimer's etiology. In contrast, a patient of advanced age with only short-term memory decline can usually be safely managed without additional imaging.

Treatment

Prevention and Early Detection

The best evidence for preventing or delaying onset of mild cognitive impairment and subsequent dementia supports healthy diets, exercise, and good cardiovascular health [1, 9, 10]. Vigorous exercise has also been shown to increase hippocampal volume in short-term studies. Hippocampal shrinkage is one of the prominent biomarkers for early Alzheimer's. The likely mechanism is increased levels of *BDNF (brain-derived neurotrophic factor*) through exercise [10]. This reinforces the key role of family physicians in promoting healthy lifestyles for patients of all ages to reduce risk for a wide range of serious diseases. There are no medications shown to reduce risk of developing MCI or preventing its progression to dementia [1].

Medications

Cognitive Enhancers: The most commonly used medications are cholinesterase inhibitors (CIs). These include donepezil, rivastigmine, and galantamine. They have at most modest benefit on symptoms with no disease-modifying activity. There is no effect on delaying the progression of MCI to dementia or prevention of the most devastating aspects of end-stage disease [1]. A targeted literature review of CIs and memantine was used for the 2008 American Academy of Family Physicians (AAFP) and American College of Physicians (ACP) clinical guidelines. It concluded that the average change in cognitive score (on MMSE or other tests) with *donepezil* was "statistically significant but not clinically important" ([11], p. 372). There may be a small subset of patients with clinically significant improvement. There was no significant difference between the CIs [11]. It reached the same conclusion about lack of clinically important improvement on cognitive testing for memantine ([10], p. 375). More effective cognitive enhancers have not been introduced since 2008. There is evidence for modest improvement in behaviors and functional status in some studies. The clinical significance of this is also not clear [11]. CIs are used primarily for AD and LBD. They have no benefit in FTD, and they may even increase agitation [8].

Current guidelines suggest that these medications can be offered on an individualized trial basis if the patient/family desires it after discussion of their limited benefits, potential side effects, cost, and the patient's overall prognosis [11]. If the patient and/or family desire a trial, they should be reassessed after several months. If there is no apparent benefit per patient or family and improvement or stabilization on an MMSE or other test is not verified, discontinuation should be considered.

Common side effects of *donepezil* and other CIs are GI related, including dyspepsia and poor appetite. There is also an increased risk of syncope [3]. A common conundrum involves a patient

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with dementia on a CI with poor appetite and weight loss. Is it due to the medication or disease progression? A trial of medication discontinuation should be considered.

Memantine is FDA indicated for moderate to severe dementia. Adding this to donepezil or other CIs has been a common practice. Adding memantine to donepezil did not improve effectiveness in the largest study to date [12]. Common side effects of memantine include headache, confusion, and hallucinations. Like the side effects of CIs, these may be difficult to differentiate from disease progression. A trial of discontinuation should be considered if these occur. Vitamin E has been used, but studies of its benefit have been inconclusive [13].

Antipsychotics: These should be used rarely in dementia due to concerns about serious side effects such as sedation, falls, confusion, and limited evidence for efficacy [3]. There is now an FDA black box warning of an increased risk of death among those using antipsychotics for dementia-related behavioral disturbances. However, they can be helpful in patients having severe distress from delusional agitation or psychosis that does not improve with other interventions. They should be used with extreme caution in patients with LBD/PDD, who frequently have severe neuroleptic sensitivity due to their dopamine deficiency from Parkinson's.

Antidepressants: Selective serotonin reuptake inhibitors (SSRIs) have better evidence for treating "agitation" than antipsychotics [14]. Depression is common in all patients with incurable serious health problems which may explain some of their effectiveness. They also have antianxiety effects. *Citalopram* has the best evidence for efficacy [14]. There is a theoretical concern for QT prolongation with citalopram, so the FDA recommends that doses above 20 mg a day not be used in the elderly. Sertraline is an alternative if QT prolongation is a concern. *Trazodone* has been shown to help with sleep cycle disturbance [15]. Tricyclic antidepressants should be avoided in most patients due to higher rates of sedating and anticholinergic side effects.

Anxiolytics: *Benzodiazepines* should be used with extreme caution due to increased confusion and fall risk [3]. A short-acting medication such as lorazepam can be useful in limited settings such as before personal care for patients who become severely distressed or physically combative during bathing or dressing in spite of non-pharmacological interventions. It is also helpful for restlessness and anxiety at the end of life. *Buspirone* is non-sedating and a much safer alternative to benzodiazepines in nonterminal patients. It has been shown to be effective in treating behavioral disturbances in dementia [16].

Hypnotics: *Melatonin* is the body's natural sleep hormone and should be first-line therapy. Effects are not as dramatic as with sedating medications, but there is a much better safety profile and no risk of dependence. It is more effective given nightly, 1–2 h before sleep, rather than as needed. Trazodone is generally the next-line treatment if needed. Zolpidem and similar hypnotics have adverse effects in the elderly similar to benzodiazepines and should be avoided. Antihistamines including diphenhydramine have similar risks, as well as more adverse anticholinergic effects [3].

Behavioral/Psychological Issues

Disruptive or distressing behaviors eventually develop in most patients with dementia. The most challenging issues for many families and other caregivers are wandering, agitation, incontinence, and disrupted sleep patterns. There are behavioral and environmental interventions which can be very helpful (Table 3). Medications should be a last resort.

Anticipatory guidance by their physician early in the disease process can help families prepare to access community and other resources which will help improve care and reduce caregiver stress. Families often benefit from counseling to help deal with grief about losing the loved one they knew before dementia changed them so much. Spiritual and psychosocial support is available to patients and families in all hospice programs.

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Table 3 Management of *behavioral issues in dementia*

1. **"Agitation"** should prompt a search for an *unmet need* (such as pain, need for toileting, constipation, thirst, hunger, urinary retention, fear, or loneliness) before considering treatment with medications. Fear of bathing, showering, or being undressed by a "stranger" is especially common. Allowing the patient to have as much control as possible over how and when this will be done is helpful Psychotropic medications should be reserved for delusional agitation not amenable to behavioral strategies and which causes severe distress or potential physical harm to the patient or caregiver. Buspirone is a safer alternative with proven effectiveness [16]
2. **Wandering** behaviors will occur at some point in most patients. Environmental modifications to allow safe walking in an enclosed area and daily vigorous exercise are the most effective interventions. Safe return bracelets are recommended for all ambulatory patients. Medications are of no benefit Searching for a dead spouse or other relative is common and should be redirected to a positive conversation about that person. Trying to convince the patient that their spouse or parent has died is usually counterproductive
3. **Incontinence**: Most patients with dementia have *functional incontinence* due to loss of cognitive awareness about needing to use or find the bathroom. Treatment should be scheduled toileting, with adult briefs as a backup measure. Overactive bladder medications do not address the root cause. They also have potentially serious anticholinergic side effects
4. **Sleep:** Nighttime awakening and wandering are stressful for caregivers and often prompt a request for sedating medications which should be avoided due to adverse side effects (see "Beers List"). Melatonin is safe and usually has modest benefit in establishing a more regular sleep cycle. Avoiding daytime naps, vigorous exercise, and not going to bed early are the most effective interventions. Families should be educated about the normal decline in hours of sleep needed with aging (average of 6–7 h a day for people >80)
5. Support groups are a valuable resource for family education and support in dealing with challenging behaviors and other dementia care issues. Early referral to the local *Alzheimer's Association* or other support groups should be strongly considered

End-Stage Dementia

Recent research has demonstrated that progressive dementias have a disease trajectory that is similar to other terminal illnesses such as advanced cancer [17]. Prior discussion of the goals of care by the family physician is instrumental in avoiding non-beneficial and potentially uncomfortable and emotionally distressing interventions in hospitals or other settings as the disease progresses [18, 19]. Difficult decisions about life support or hospital transfers are often faced in a nursing home or hospital. Whenever possible, the family physician should try to provide care or support in those settings directly as attending physician or via a social visit or phone call. Specific management issues are detailed in Table 4.

Summary

Family physicians will see increasing numbers of patients with dementia as our population ages. They are well suited to evaluate and manage the majority of patients with dementia. Referral to subspecialists for ongoing care has not been shown to improve outcomes [22]. It should be considered in atypical cases where the diagnosis is in doubt.

Routine cognitive screening is a required component of Medicare Wellness Visits. This will help family physicians improve early detection and prompt evaluation for reversible causes. Most cases unfortunately will not be reversible. Efforts should then focus on family education and preventing complications of dementia. Avoiding adverse medication effects and promoting exercise to help reduce *falls* and disruptive behaviors are effective low-cost interventions.

A cornerstone of family medicine is the universal promotion of healthy diets and exercise for disease prevention. These, along with cognitive stimulation, are currently the most effective interventions for delaying the onset and progression of most dementias. The use of imaging or other biomarkers to detect early or preclinical dementia may become important in the future if disease-modifying medical therapies become available.

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Table 4 Management of end-stage dementia. End-stage dementia is characterized by loss of interest in food, difficulty in recognizing family members, and increased susceptibility to aspiration pneumonia and other infections. It is now generally recognized as a terminal disease process [17]

1. Early discussion of goals of care	All adults should be encouraged to prepare an *advance directive* while mentally competent. It should include their wishes about care if a terminal illness develops. This should include wishes about life support including tube feedings if advanced dementia develops. This will prevent family distress when facing these decisions without knowing their loved one's wishes [18] Education about the ultimately terminal course of neurodegenerative dementias such as Alzheimer's should be included in this discussion. Many forms are available to facilitate this, such as Five Wishes. Goals of care should routinely be reviewed in Medicare Wellness Visits or other venues if not yet established
2. Nutrition	*Feeding tubes* have not been found to be of benefit in advanced dementia and do not prevent aspiration [20]. Impaired swallowing signals a very poor prognosis, and focus should shift to pleasure feedings and other comfort measures. Sweets and cold, soft foods such as ice cream are usually best appreciated and tolerated at this stage Orders such as NPO (nothing by mouth) should be avoided as this may lead to a misperception by families that we are "starving" the patient. "Pleasure feeds as tolerated" is a preferred alternative. Mouth swabs with fluid of choice should be offered in the final stage. This can be especially comforting for family members Education should focus on the fact that not eating is part of the natural course of the disease and the body responds by shutting down bodily functions including the thirst center. The body begins producing endorphins (natural opioids) to help transition to a comfortable death
3. Hospitalizations	Hospitalizations of nursing home patients with advanced dementia for pneumonia or other complications are common and have not been shown to improve outcomes. They are associated with worsening confusion and debility while in the hospital. Treatment at the nursing facility after discussing the risk/benefits of hospital transfer with the family is generally recommended
4. Hospice/palliative care	*Hospice* care improves pain and other comfortable dying measures in end-stage dementia [21]. Patients meet hospice criteria when life expectancy is <6 months as evidenced by loss of interest in food with weight loss, recurrent infections, skin breakdown, multiple falls, severely diminished speech and understanding, or other dementia complications

Early discussion of patient and family goals of care regarding their wishes if dementia progresses is critical to avoiding unwanted burdensome care in end-stage disease. Hospice or other comfort-focused care support is strongly recommended when this stage is reached to help reduce patient and family suffering.

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Elder Abuse

25

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General Principles

Definition and Background

Elder abuse is generally defined as the maltreatment of individuals over the age of 60 [1]. The World Health Organization (WHO) recognizes elder abuse as "a single, or repeated act, or lack of appropriate action, occurring within any relationship where there is an expectation of trust which causes harm or distress to an older person" [2]. Instances of abuse toward older adults perpetrated by a stranger (e.g., theft, fraud) are therefore not considered elder abuse [3]. Elder abuse can be of various forms: physical; psychological/emotional, sexual; financial and material abuse; abandonment; neglect; and serious loss of dignity and respect [4].

The American share of the older population over 65 is expected to increase from 16.6% in 2020 to 22.4% by 2050 [5]. Similarly, the global share of older people is projected to increase from 9.3% in 2020 to 15.6% in 2050 [5]. In parallel,

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aging of the global population will likely result in an increased prevalence of elder abuse around the world [1, 3, 6]. Global prevalence rates of overall elder abuse were reported to be 10–15.6% and 34% for self-report and third-party reports, respectively [7, 8]. Geographical differences were seen in those prevalence estimates with the highest rates in Asia at 20.2%, moderate numbers in Europe at 15.4%, and a lower reported prevalence in the Americas at 11.7% [1, 8]. However, these estimates may be inaccurate due to the lack of clear definitions, reporting guidelines, and reliance on self-reports from those who are able to participate in surveys. This may exclude vulnerable patients who are at greater risk for mistreatment [1]. Thus, a busy family physician caring for older adults is likely to encounter victims of elder abuse on a regular basis.

Disturbingly, only 1 in 23 cases of elder abuse were reported to Adult Protective Services (APS) agencies and fewer than 2% of reports and neglect came from physicians, suggesting that physicians may lack training, experience, education, and adequate guidelines for the assessment and management of abuse [9, 10].

Elder abuse causes fear, depression, stress, isolation, sleep disorders, disability, and increases the risk for suicide and death. Victims of abuse have a mortality rate three times higher than non-victims [3, 9, 11].

Despite growing awareness and concern regarding elder abuse, the US Preventive Services Task Force (USPSTF) concluded in 2018 that the current evidence was insufficient to assess the balance of benefits and harms of screening for abuse and neglect in all older or vulnerable adults. Further, The USPSTF found no valid reliable screening tools in the primary care setting to identify abuse of older or vulnerable adults without recognizable signs and symptoms of abuse [12]. The American Medical Association, on the other hand, encourages physicians to inquire about abuse routinely. The National Center on Elder Abuse suggested that primary care settings may provide a valuable opportunity for elder abuse screening as elders are frequently seen for common conditions associated with aging [13, 14]. Despite the discordance in screening guidelines, physicians might be confronted with situations that arouse suspicions of abuse [15].

This chapter discusses the definitions of abuse, risk factors for abuse associated with both the elderly and their caregivers, barriers that elderly patients and their physicians face when dealing with abuse issues, assessment of suspected elderly abuse victims, reporting guidelines, and prevention strategies.

Categories of Abuse

The Centers for Disease Control and Prevention (CDC) and a diverse group of elder abuse experts collaboratively produced version 1.0 of uniform definitions and recommended core data elements of the major types of elder abuse as follows [4, 9]:

Physical abuse: The intentional use of physical force that results in acute or chronic illness, bodily injury, physical pain, functional impairment, distress, or death. This includes pushing, slapping, kicking, spitting, hitting, misusing medications, force feeding, and using restraints. These physical acts may cause bruising, cuts, lacerations, sprains, hair loss, missing teeth, fractures, burns, and other traumatic injuries.

Sexual abuse: Forced and/or unwanted sexual interaction (touching and non-touching acts) of any kind with an older adult. It includes rape, unwanted touching, sexual advances, or innuendo. Victims may suffer from trauma around the anus, vagina, breasts, and mouth.

Emotional/psychological abuse: Verbal or nonverbal behavior that results in the infliction of anguish, mental pain, fear, or distress. It includes humiliation/disrespect, threats, harassment, isolation, or coercive control. Threats to institutionalize or withhold medication, nutrition, or hydration are also included in this category. Victims often display feelings of depression, withdrawal, and apathy.

Financial abuse/exploitation: The illegal, unauthorized, or improper use of an older individual's resources. This includes, but is not limited to, depriving an older individual of rightful access to, information about, or use of personal benefits, resources, belongings, or assets. It consists of overpayment for goods or services; unexplained

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changes in power of attorney, wills, or legal documents; missing checks or money; or missing belongings.

Neglect: Failure to protect an elder from harm or the failure to meet needs for essential medical care, nutrition, hydration, hygiene, clothing, basic activities of daily living or shelter, which results in a serious risk of compromised health and/or safety, relative to age, health status, and cultural norms. Neglect may be intentional or unintentional, and it might also occur within retirement homes, assisted living facilities, nursing homes, and hospitals [15] .

Self-neglect: Is frequently omitted or reported separately in statistical summaries. It has been described as "the behavior of an elderly person that threatens his/her own health and safety." It is not unique to seniors and it might be reflective of problems that fall outside the realm of elder abuse [15].

There is some disagreement in the literature as to the most common form of elder abuse. Nonetheless, recent meta-analyses have shown that emotional abuse was the most common, followed by financial abuse, neglect, and then physical abuse [1, 7, 8]. Sexual abuse was the least often reported, likely due to failure to screen for or lack of disclosure by victims [1, 7, 8]. Cultural or regional differences might have been found in incidence and reporting of the abuse subtypes due to differences in cultural norms that in turn could influence abuse perception and outcomes. However, a possible association between elder abuse, culture, and ethnicity is inconsistent across the literature [16].

Risk Factors

Evidence supports a multifactorial etiology of elder abuse involving victim vulnerability and perpetrator risk factors, and factors related to their relationship and the environment [1, 3, 17].

Victim vulnerability factors: Dependency, poor physical health, cognitive impairment, low socioeconomic status, gender, age, and race/ethnicity are some of the most commonly cited vulnerability factors [1, 18]. Dependency can be functional, financial, social, or emotional in nature [3]. Physical and cognitive disability have been associated with a greater risk of elder abuse as they impair their ability to seek help, impair decision-making capabilities, and limit autonomy [19]. Patients with dementia are more likely to be victims of financial exploitation [9, 20]. Women are more likely to be victims of abuse as they have a longer lifespan that might increase their risk of dependence and cognitive impairment in old age [1, 7, 18]. Elder abuse is also more common in minority older adults compared to whites [21]. In particular, older lesbian, gay, bisexual, and trans (LGBT) people are more likely to have known vulnerability factors, such as loneliness, lower likelihood to be partnered and to have children, which puts them at higher risk of abuse compared to their heterosexual peers [22].

Perpetrator risk factors: Perpetrators are most likely to be adult children or spouses, and they are more likely to be males, to have a history of substance abuse, to have mental or physical health problems, to be socially isolated, to have financial problems with dependence on the victim, and to be experiencing major stress especially caregiver burnout and poor coping skills [1, 15, 18].

Relating to the relationship: A conflictual relationship between the victim and the perpetrator has been consistently identified as a vulnerability factor for elder abuse [3].

Relating to the environment: Lack of social support, living with a larger number of household members other than a spouse, and living in a facility rather than in the community are associated with higher rates of abuse [1, 3].

A good screening history by the family physician is needed to uncover a possibility of a neuropsychiatric disease in the victim, and to reveal a potential perpetrator especially if the caregiver becomes exhausted and overwhelmed over time.

Challenges to Identification

Patient-Related Challenges

Victims of elder abuse usually face many obstacles when disclosing abuse because it is being perpetrated primarily behind closed doors and by family members. Some patients have physical or

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cognitive barriers or are socially isolated which not only renders them at risk of abuse but also makes their recognition challenging [23]. Other barriers to seeking help include fear of consequences for self and the perpetrator, especially if it is a close family member; victims might be afraid of retaliation or worsening of the abuse and their relationship with their family, of being abandoned, isolated, or institutionalized [24]. They also might be physically frail or have socioeconomic dependency on the perpetrator in addition to feelings of shame and embarrassment, self-blame, low self-esteem, helplessness, and the stigma associated with seeking help [9]. Also, they may have doubts about the capacity and adequacy of services to help them, a lack of trust in professionals, and accessibility were some other barriers reported [23, 24].

Physician-Related Challenges

The challenges doctors face in detecting elder abuse are mainly due to lack of awareness about elder abuse and its prevalence [25]. Many physicians may not be able to detect the signs of elder abuse, much less how to screen for it, and especially ascribing the subtle signs of abuse to the vicissitudes of "normal" aging [26]. Ageism acts as a type of prejudice that both justifies abusive behavior against older people and leads to overlooking the consequences it has on them. It impedes the prevention and early identification of elder abuse [26, 27]. Fear of legal and ethical consequences are not to be disregarded especially when the victim is not willing to share information with the authorities [25, 28]. Training family physicians to screen for risk factors contributes to early detection and intervention and thus prevents further abuse [9].

Assessment

History and Physical Examination

Family physicians may have well-established relationships with older adults and their families that allow them to recognize potential abuse provided that they maintain a high level of suspicion. They should work with multidisciplinary teams to ensure thorough assessment, intervention, and follow-up of elderly patients [29].

During the consultation, it is helpful to interview the patient and caregiver together and separately to detect disparities offering clues to the diagnosis [30]. Interviewing the victim alone helps mitigate the fear of retaliation and shame that might otherwise hinder disclosure [10]. If a language barrier exists, a professional translator should be used rather than the caregivers or family members [30].

A complete history is the key; it should start with open-ended questions such as "Can you tell me what happened?" and further questions should be neutral and nonjudgmental to encourage patients and caregivers to provide detailed information [10]. The history should focus on current health status, living arrangements, emotional stressors, social support, medication review, and financial status [30]. All vulnerability and risk factors for abuse should, also, be inquired about as well as the patient's functional status, cognition, care needs, and safety of the home environment [10, 30]. Screening for depression and social isolation should not be overlooked [31].

Behavioral signs that may offer clues that suggest elder abuse include poor eye contact, anxiety, low self-esteem, and helplessness [30]. A caregiver who often interrupts the patient to answer questions for him or her or appears reluctant to leave the patient alone might be a potential perpetrator [30, 32]. Nonetheless, interruptions during history taking may be compensatory for the patient's cognitive impairment and do not always indicate abuse [10]. Moreover, physicians should be able to differentiate signs of injuries from disease processes and normal aging. These include allergic reactions, osteoporotic fractures, vaginal bleeding due to atrophy, and anorexia caused by mental illness [10, 19].

The physical examination should be comprehensive, with the patient completely undressed in order to perform a full dermatological evaluation including fingernails and toenails [30]. The clinical manifestations of elder abuse are difficult to

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identify and vary by type of abuse. However, general signs suggestive of abuse and neglect might include signs of dehydration and malnutrition, poor hygiene and physical care, and signs of psychological distress [19].

Patterns of injury such as ligature marks, multiple burns and bruises, of different sizes and ages, found on the abdomen, neck, posterior legs, or medial arms, as well as the presence of unusual or unexplained fractures are suggestive of physical abuse, whereas sexually transmitted infections, unexplained vaginal/rectal bleeding or pain in the oral or anal–genital regions are suggestive of sexual assault that mandates forensic examination [10, 16]. Mobility assessment helps ascertain the actual cause of injuries from reported falls, while cognitive assessment using the Mini-Cog test helps screen for a possible dementia [10, 19, 33].

The comprehensiveness of the physical examination should be coupled with a meticulous documentation of all findings including the patient's statements, behavior, appearance, and body charts or clinical photographs of the location and morphology of injuries [10, 29].

Radiographs should be obtained when possible if fractures are suspected along with a CT scan if the patient has suffered a head injury. If clinical findings suggest malnutrition, then laboratory testing (e.g., complete blood count, blood urea nitrogen, creatinine, total protein, and albumin levels) should be requested to document consistent findings [19]. Serum drug levels help uncover possible poisoning, under treatment or inappropriate use of medications [10].

Management and Reporting Guidelines

Despite the presence of several tools that have been validated for elder abuse evaluation and management, there is currently no gold standard tool [14, 32]. The Elder Abuse Suspicion Index (EASI) was validated in a primary care setting to screen for abuse in cognitively intact patients. The EASI has five patient-answered items, plus one physician question with a marginal sensitivity of 0.47 and a specificity of 0.75 [14, 15, 34]. Figure 1 shows a suggested algorithm for the management of suspected elder abuse.

A positive screen for elder abuse does not unequivocally indicate abuse, but it mandates referral for complete multidisciplinary functional assessments that may include home visits by local social workers, concerned family or friends, or Adult Protective Services (APS) authorities [1, 10]. Importantly, clinicians do not have to prove that elder mistreatment has occurred; they need only document a reasonable cause to suspect that it has [29]. After that, physicians need to ensure safety of the victim and report the case. Reporting is not federally mandated but is regulated by state governments; nearly all states have enacted mandatory reporting laws whereas pertinent statutes may vary [29]. Failure to report, however, can be considered negligence and is potentially punishable by fines, imprisonment, or loss of license [19]. Providing educational material for patients and families that includes a description of the warning signs of caregiver stress and available community supportive services is also an effective reporting approach. Even when law enforcement becomes involved, family physicians still bear significant responsibility for follow-up medical care of patients [10].

Online resources available to assist physicians with elder abuse include Eldercare Locator (https://eldercare.acl.gov/Public/Index.aspx), the Administration on Aging, American Medical Association, and the National Centre on Elder Abuse [10, 14].

Prevention

Elder abuse is a complex, multifaceted problem, and preventive strategies should be applied at many levels including public education and awareness. Early multidisciplinary intervention and education on resources and community support can be implemented to preserve elders' emotional well-being [9, 35, 36]. Home care clinicians can play an important role in prevention through astute observation of patients, their behaviors, and environment which alerts clinicians to potential abuse [9].

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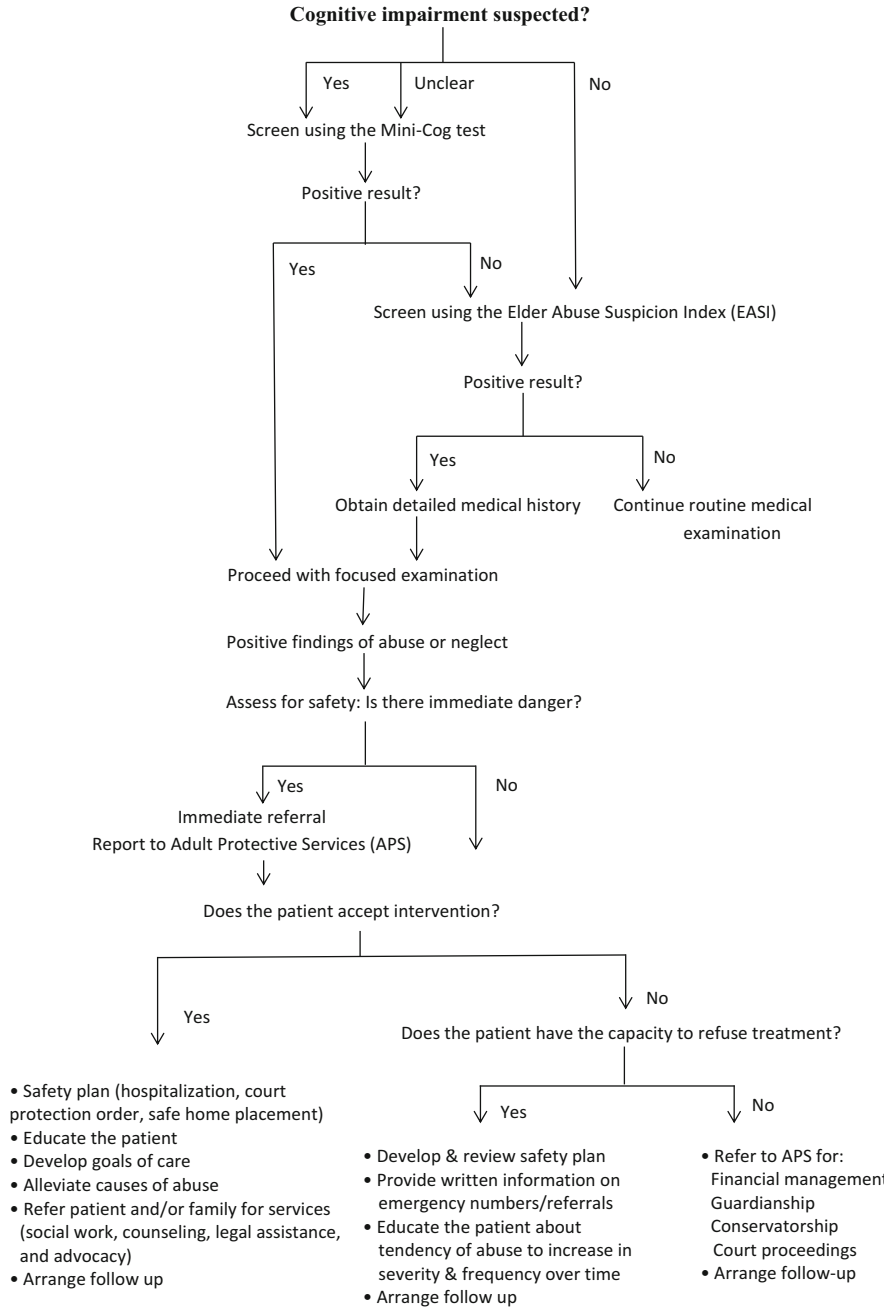


Fig. 1 Management of suspected elder abuse (Adapted from Refs. [10] and [29])

Conclusion

Family physicians may have well-established relationships with older adults and their families that allow them to recognize potential abuse and neglect [29]. They are likely to encounter elder abuse in their practice, hence early identification and intervention are essential to avoid catastrophic events and to save lives.

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Care of the Very Elderly

26

Karina Isabel Bishop

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It is estimated that the number of people over 65 will surpass the estimated number of children under 18 for the first time in 2030 worldwide [1]. A deficit in the number of geriatricians will make treating older adults part of any primary care physician's practice.

When caring for older adults, assessment of functional ability is critical. Function gives the physician a picture of the interaction between medical conditions, physical aging, cognition, and overall health in the setting of the patient's environment. Function is a predictor of mortality, a reflection of a patient's level of independence, and often corresponds to their quality of life [2]. Knowing a person's baseline functional abilities also allows the physician to recognize when there is a change in their condition. However, physicians often do not recognize the importance of functional disabilities in their patients. At times, disease management is less important than maximizing patient function. In the same way, understanding a patient's functional status is the only way to assess the patient's resource needs and appropriate level of care.

Functional Impairment of Older Adults

Sensory Impairment

Older patients commonly have decreased sensory awareness, commonly evidenced by vision and hearing loss. Hearing loss is most common in

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the high-frequency range and is usually bilateral. Hearing loss can lead to isolation, depression, and avoidance of social events.

The whisper test is an accurate and simple office screen for hearing loss [3]. Standing behind the patient at arm's length (about 2 feet), have the patient cover the untested ear, fully exhale (to control for the loudness of the whisper), and whisper a combination of three numbers and letters (e.g., K-4-2). Then ask the patient to repeat the set. If unable to repeat correctly, a second set is whispered. If unable to repeat at least three of the possible six numbers or letters, the test is considered positive for impairment. If the patient fails the whisper test screening or if the patient acknowledges hearing loss, the next step is evaluation for occluding cerumen. If present, one should retest after removal. If the screen is failed again, the provider should offer referral to audiology for definitive diagnosis and treatment.

Visual impairment can be assessed by asking questions regarding driving, reading, and assessing for falls. When examining visual acuity, make sure to use the patient's corrective lenses. Using a Snellen chart (far vision) or Rosenbaum card (near vision), those scoring worse than 20/40 is the cutoff for visual impairment [4]. A quick medication review looking for drugs that can be associated with blurry vision (such as amiodarone, sildenafil, tamoxifen, and anticholinergics) should be performed. Remember that patients over 65 should get a full eye exam biennially (yearly for those with diabetes) for early detection of conditions causing visual impairment.

Nutrition

Poor nutrition in the elderly is often overlooked by physicians unless they maintain a high index of suspicion for this condition. If available, weight and height should be compared to the year before. Unintentional weight loss of >5% in 6 months or a low BMI should trigger a nutritional assessment. A careful history can often indicate why a patient is losing weight. Mechanical causes, like ill-fitting dentures or a dry mouth, as well as social causes, like eating alone or not being able to leave the house to get groceries or being unable to cook meals, may provide insight into a patient's concerning nutritional status. Also, ask about economic barriers in securing food and the use of community services such as Meals on Wheels, senior centers, or church-delivered food. The use of the two-question screening tool "Hunger Vital Sign" helps flag those with food insecurities. Ask if within the past 12 months the patient worried whether food would run out before they got money to buy more or if the food they bought just didn't last and they didn't have money to get more. A positive answer to either of these questions indicates food insecurity. Making a connection to the local agency on aging usually provides meal resources that can be relayed to patients. Looking into the Supplemental Nutrition Assistance Program (SNAP), formerly called Food Stamp Program, can also help those with lower income. Requirements vary by state. Reviewing for medications and conditions that can lead to weight loss, including digoxin, cholinesterase inhibitors, SSRIs, amiodarone, and topiramate, and screening for depression are important. Nonpharmacologic treatments for weight loss in older adults include removing specific (often unpalatable and sometimes unaffordable) diets (low sodium, low fat); adding between meal snacks; increasing calorie density of foods; arranging for shopping trips, cooking times, and feeding assistance if needed; and attending group meals to avoid social isolation. No medications are FDA-approved to promote weight gain in older adults.

Mobility

In older individuals, causes of falls are often multifactorial. Asking about falls (if yes, how many), fear of falling, and feelings of unsteadiness, as well as assessing for associated symptoms like dizziness or presyncope or pain that impairs mobility, can help the clinician uncover the more obvious causes. Asking about the use of assistive devices, canes, walkers, and wheelchairs is also

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important. Checking medication lists and potential culprits like tricyclic antidepressants, benzodiazepines, sedatives, opiates, anticonvulsants, antipsychotics, antiarrhythmic, antihypertensive, and diuretics as well as using screening tools like STEADI [5], which includes the Timed Up and Go, can help guide appropriate interventions for fall prevention.

Mood

Recognizing and diagnosing late-life depression can be difficult. Complaints like lack of energy or other somatic symptoms like poor sleep, gastrointestinal complaints, and fatigue are common. Oftentimes patients will neglect to mention these to their providers. Screen all patients for depression with the Patient Health Questionnaire-2 [6]. It includes the following two questions:

- In the past 2 weeks, have you had little interest or pleasure in doing things?
- In the past 2 weeks, have you often been bothered by feeling down, depressed, or hopeless?

A positive screen is followed up with a more in-depth assessment, usually a Patient Health Questionnaire-9 or the 15-item Geriatric Depression Scale [7]. Always consider that depression may be a primary condition or associated with comorbid illnesses such as dementia. In the absence of suspicion for a specific condition, checking thyroid levels, B12, electrolytes, liver and kidney function tests, complete blood count, and a urinalysis is a reasonable workup for secondary causes. Patients suffering from subsyndromal depression (those with symptoms that do not meet full DSM criteria) deserve special mention. These patients should be monitored carefully, since the disease can present itself at any time and then require management. Treatment options include cognitive behavioral therapy, problem adaptive therapy for those with mild dementia, SSRIs, and SNRIs. Avoid paroxetine and fluoxetine in the elderly, as these are more anticholinergic.

Sleep

The idea that older adults require more sleep than young adults is a common misconception. It is perfectly acceptable for an older adult to sleep 5–7 h or as much as 12 h without concern, as sleep patterns naturally change as we age. Asking about bedtime routines and latency time before falling asleep (it takes longer for older adults to fall asleep), as well as nocturia and presence of naps, will often provide clues to the underlying causes of sleep problems. Screening and evaluation for appropriate treatment for sleep apnea should also be performed if this is a possibility. Sleep hygiene strategies (Table 1) can be emphasized as first-line treatment. If medications are prescribed, using the lowest effective dose and combining with behavioral treatment are preferred. Be aware these medications increase the risk of falls and hip fractures. Over-the-counter antihistamines should never be used to treat insomnia in older adults. Consider using SSRIs or buspirone for those with anxiety at bedtime. If a medication is required for sleep, short-term use or intermittent use is preferred.

Table 1 Sleep hygiene strategies

Sleep hygiene strategies
1. No caffeine or other stimulants after lunch
2. Alcohol in moderation and none after dinner
3. No smoking in the evening
4. Exercise (not excessive and not just before retiring) and get sunshine during the day
5. Have a pure carbohydrate snack (cake, cookie, candy) 15–20 min before heading to bed
6. Use bed (and bedroom) only for sleeping
7. Go to bed only when sleepy. Do not set a regular time for going to bed in the evening; go to bed only when you are tired and sleepy
8. If still awake after 30 min, get up, go to another room, engage in interesting or useful activity until sleepy again, and then return to bed. If still unable to sleep in 30 min, repeat as often as necessary
9. Get up at the same hour every morning
10. Avoid daytime or early evening naps
11. Keep the bedroom cool, quiet, and dark in the evening and night

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Continence

Urinary incontinence can be evaluated by asking about changes in bladder habits, specifically problems with leakage, frequency, or urgency. In older adults, it is most often multifactorial, but eliciting the primary component if possible (urge, stress, overflow) may be helpful to determine specific evaluation and treatment. Red flags like hematuria and pelvic pain should be referred for urological evaluation after excluding urinary tract infection. Patients with frequency and urgency but without urinary incontinence should be treated for overactive bladder. The use of tools like the International Prostate Symptom Score [8] can quickly help with diagnosing prostatic obstruction problems, which are often present in older men. Examining functional status (including mobility); assessing for bladder distension, cord compression symptoms, presence of edema, and prostate consistency in men; and checking for phimosis, paraphimosis, or balanitis and for atrophic vaginitis and rectocele or cystocele or prolapse in women will be helpful in determining a cause. Assessing mental status, which is particularly important for planning appropriate treatments, will also prove beneficial. Testing includes review of a "bladder diary" where the patient records time and volume of continent and incontinent voids, as well as jotting down oral intake. Measuring post-void residuals (preferably with a bladder scanner instead of a catheterization) and a basic urinalysis are the usual first steps of evaluation. Next steps usually include urodynamic studies if the diagnosis remains unclear. Treatment strategies include ensuring adequate access to toileting, including commodes or urinals, prompted voiding in those with cognitive impairment (asking if a patient needs to void, taking them to the bathroom starting at 2–3 h intervals, and praising when continent and responding to toileting), using adaptive clothing, optimizing treatments for heart failure, controlling chronic cough, and reducing or eliminating medications that can contribute to incontinence. Decreasing consumption of caffeine and diuretic beverages and avoiding extreme fluid intake, as well as limiting fluids after supper to decrease episodes of nocturia, treating constipation, and encouraging patients to quit smoking (which produces a chronic cough), may also be beneficial. Urge, stress, and mixed urinary incontinence are also treated with behavioral therapy, particularly bladder training.

Bladder Training Instructions

1. Start by going to the toilet and trying to pass urine every 2 h while you are awake.
2. Try to pass urine whether or not you feel the need to. You must try to pass urine even if you have just been incontinent.
3. If you get a strong urge to go to the bathroom before your scheduled time:

   stop and don't run to the bathroom, stand still or sit down if you can, and relax. Take a deep breath and let it out slowly. Concentrate on making the urge decrease or even go away, in any way that you can (imagine the pressure becoming less and less).
4. Keep on this schedule until you can go 2 days without an episode of urine leakage. Then, increase the time between scheduled trips to the toilet by 1 h. When you once again are able to go 2 days without an episode, extend the time between trips again.
5. Keep this up until you can go 4 h between trips to the toilet or until you are comfortable. This may take several weeks.
6. Don't get discouraged. Bladder training takes time and effort, but it is an effective way to get rid of incontinence without medicines or surgery.

Similarly, changes in bowel habit can be difficult problems for an elder to bring up but extremely important to their perception of health. Constipation, which is usually defined as fewer than two to three bowel movements a week, straining at defecation, hard feces, or feelings of incomplete evacuation should first prompt a medication review (see Table 2) and then a search for conditions that cause constipation (see Table 2). Stopping all constipating medications, if possible, followed by increasing dietary fiber to around 20 g/day and increasing fluids to 1.5 L/day and physical activity are first steps to management of constipation. Adding an osmotic agent like

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Table 2 Medications and conditions that cause constipation

Medications that cause constipation	Conditions that cause constipation
Opiates	Mechanical obstruction
Antacids with calcium and aluminum	Dehydration
Anticholinergic drugs	Depression
Antidepressants	Diabetes
Lithium	Hypercalcemia
Antihypertensives – calcium channel blockers	Hypokalemia
Antipsychotics	Hypothyroidism
Barium	Immobility
Bismuth	Low intake of fiber
Diuretics	Panhypopituitarism
Iron	Spinal cord injury
	Uremia
	Parkinson disease
	Stroke

polyethylene glycol, followed in order by a stimulant laxative, like senna or bisacodyl, should be the next step. Docusate is not routinely used in older adults, as there is no good evidence that it is effective in that population.

Passage of three or more watery stools in a day meets the criteria for diarrhea. As always, review the medication list for potential culprits like antibiotics, laxatives, metformin, and cholinesterase inhibitors. Also check for fecal impaction and consideration of disorders like IBS, malabsorption, IBD, and infections. Lactose intolerance is also a common cause of diarrhea in older adults. If patients appear acutely ill or dehydrated, hospitalization and further testing as guided by history and physical exam are preferred, but those that do not appear seriously ill or do not have blood in their feces may wait 48 h to see if symptoms resolve. First-line treatments in the management of diarrhea in older adults include loperamide and bismuth subsalicylate.

Patients reporting diarrhea should also be questioned about fecal incontinence. This is another condition which is often multifactorial. The most common causes, aside from those mentioned above for diarrhea, include overflow from colonic distension by excessive feces causing continuous soiling, dementia, and anorectal incontinence due to a weak external sphincter (commonly seen post-surgery or in multiparity). Red flags like hematochezia or unexplained weight loss should prompt a referral to gastroenterology.

On physical exam, focusing on palpating the abdomen for colonic distension or masses and inspecting the anus for fissures, hemorrhoids, rectal prolapse, or rectocele may help determine the cause. Basic lab work includes checking thyroid levels and a metabolic panel and may include radiographs and/or endoscopy.

Cognition

There is insufficient evidence at the current time to recommend for or against dementia screening in older adults. Many patients recognize early cognitive deficits such as recall of names or item placement. Minor problems in these domains may indicate a higher than average risk for progression to dementia, but the deficits may remain stable or may resolve. It is not until they start having memory problems that affect their day-to-day activities that we can make a diagnosis of dementia. Screening with the Mini-Cog is simple. If a patient fails, obtaining a Montreal Cognitive Assessment, St. Louis University Mental Status test, or a Mini-Mental Status Exam is the next appropriate step. This, together with a history (from the patient and often from family or caregivers), physical and neurological exam gives us a better picture of the situation at hand. It is important to assess both basic activities of daily living (ADLs), which are skills necessary to get ready for the day, and instrumental activities of daily living (IADLs), which require more complex mental processes such as executive function and judgment. (Table 3). Several tools are available for use as an aid in assessing ADLs and IADLs such as the Katz index for ADLs [9] and the Lawton scale for IADLs [10]. Difficulty in IADLs may precede a decline in cognitive screening tests in persons with a developing dementia. Such a decline should prompt more thorough cognitive testing.

Concerns about driving should be addressed, including if the patient has had any driving-related problems, recent accidents, moving violations, passenger complaints, or problems with getting

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Table 3 Activities of daily living and instrumental activities of daily living

Activities of daily living	Instrumental activities of daily living
Bathing* (ADL with most prevalence of disability) Dressing Toileting/continence Transferring Feeding Grooming	Managing finances Driving Shopping Preparing meals Medication management Technology/Internet and cell phone use Housekeeping/laundry

lost in familiar areas. Any of these are red flags and may indicate a need for further examination and formal driving evaluation. Safety concerns should be discussed honestly with the patient and family, particularly if the patient lacks insight into the deficits. Suggesting a driving evaluation by an occupational therapist (OT) is a good next step for cases in which it is not clear if they should be completely off the road. While an initial OT consultation is generally a Medicare-covered service, on-the-road testing is not and costs at least $300–500 depending on location. Take into account the fact that recommending that a patient stop driving can lead to decreased activity and increased depressive symptoms.

Lab testing when cognitive decline is a concern includes a complete blood count, thyroid studies, homocysteine level, methylmalonic acid, electrolytes, liver and kidney function, HIV, and serologic testing for syphilis. Brain imaging is rarely useful but may be pursued in the appropriate setting. The primary goal of treatment is to improve quality of life and maximize functional performance by enhancing cognition, mood, and behavior.

Geriatric Syndromes

When a medical condition does not fit into a distinct organ-based disease category and is present in older adults, it is termed a geriatric syndrome. The causes of these syndromes are usually multifactorial. Examples include cognitive impairment, delirium, incontinence, malnutrition, falls, pressure ulcers, sleep disorders, sensory deficits, fatigue, and dizziness. These conditions have a major impact on quality of life for older adults and are a common cause of disability. There is a strong association between the presence of geriatric syndromes and dependency in activities of daily living [11].

The hallmark geriatric syndrome is frailty, which is defined as increased vulnerability to adverse outcomes after exposure to a stressful event. Frail older adults are less able to adapt to stressors such as acute illness or trauma than younger or non-frail older adults. This increased vulnerability contributes to a higher risk of adverse outcomes, including death. Older age itself does not define frailty; instead, multiple frailty screening tools have been developed and utilized for risk assessments. Frailty tools are increasingly used to identify patients at highest risk of adverse outcomes. Common frailty models include the Physical Frailty Phenotype scale [12], the Frailty index, and the FRAIL scale [13].

End of Life and Goals of Care

It is never too early to begin advance care planning and a discussion about goals of care. Choices need to be made about what outcomes are important to patients, and this is often more useful when the patient is able to provide input and the cognitive capacity to express these wishes. These discussions should include determination of surrogate decision-makers (appointing a durable power of attorney to serve as a surrogate in the event of personal incapacity) and also clarifying and articulating patients' values over time. Advance directives are useful to help guide therapy if a patient is unable to speak for himself. Tools like Do Not Resuscitate orders, Physician Orders for Life Sustaining Treatment (POLST), and Living Wills are useful for reference and possibly to fill out when having these conversations. Specifically mentioning what the patient's wishes are in regard to resuscitation procedures, mechanical ventilation, chemo and radiation therapy, dialysis, blood products, and pacemakers can help guide decision-making in difficult times.

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When a serious life-threatening disease appears and end of life is near, robust measures are taken to optimize the quality of life by anticipating, preventing, and treating suffering. These measures, also known as palliative cares, have been shown to improve patient the quality of life remaining and outcomes and should be recommended without reservation.

Hospice care is palliative care provided by an interprofessional team for patients who no longer seek disease-modifying treatments, but instead prefer to allow the disease to take its normal trajectory. In the United States, a patient must have a prognosis of less than 6 months to live in order to qualify for this service.

Both palliative care and hospice care manage common end-of-life symptoms like pain, delirium, anorexia and cachexia, anxiety and depression, bowel obstruction, constipation, cough, dysphagia, dyspnea, excessive secretions, nausea, vomiting, skin failure, and fatigue.

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Part VI

Family Conflict and Violence

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Child Abuse and Neglect

27

Suzanne Leonard Harrison and Mary Pfost Norton

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Introduction

Child maltreatment is a public health emergency that impacts the physical, emotional and cognitive development of affected children. The impact is not limited to childhood, as significant adverse events during childhood affect adult health with an increased burden of disease and risk of early death [1]. The Centers for Disease Control and Prevention (CDC) defines child maltreatment as any act or series of acts of commission or omission by a parent or other caregiver that results in harm, potential for harm or threat of harm to a child [2]. Maltreatment can be classified into abuse or neglect, and the majority are victims of neglect. However, at least 15% of reports contain two or more maltreatment types [3]. The economic burden of child maltreatment was estimated at $428 billion in 2015 [4].

In 2018, there were more than 3.5 million reported cases of child maltreatment in the United States, with 678,000 victims confirmed. Of these victims, there were an estimated 1770 fatalities [3]. The CDC estimates that one in seven children have experienced child abuse and/or neglect in the past year and this is likely underreported [5]. The highest rate of victimization occurs in the first year of life. While girls are victimized at a higher rate than boys, the fatality rate for boys is higher. Child maltreatment occurs in families of all backgrounds. However there exists a racial disparity in both victimization and fatalities, with American Indian, Alaskan Native and African American children subject to child abuse and neglect at higher rates than Caucasian and Hispanic children [3]. While the association between child physical abuse and poverty is strong [6], clinicians should be careful to avoid premature judgment of the parent or caregiver based on their appearance, ethnicity, or socioeconomic status.

Prevention

Child maltreatment is preventable by enhancing support to families, addressing social and cultural norms and intervening to lessen harms or prevent future risk to children [5]. Children younger than three, those with disabilities, chronic illness or mental health issues are at increased risk for maltreatment. Parents with a personal history of child maltreatment, substance abuse or mental illness are at increased risk for abusing or neglecting their own children. Low income, low level of education, young age of parents, non-biological caregivers in the home and family stress have all been associated with increased risk (Table 1). Other significant risk factors include under resourced communities, violence in the community, presence of intimate partner violence in the home and social isolation [7]. Inadequate parenting skills are an important component of risk and can be mitigated by education that focuses on child-parent relationships, age-appropriate rules that reinforce good behavior, and monitoring in a supportive environment.

The role of the family physician in recognizing risk and protective factors is essential in establishing the groundwork to provide effective anticipatory guidance for families to reduce the incidence and impact of child abuse and neglect. Protective factors include strong parenting skills, a child with a robust ability to self-regulate behavior and emotional reactions, problem-solving skills and a positive school environment. It is imperative that the tenets of trauma-informed

Table 1 Risk factors for child maltreatment

Parent or caregiver	Child
Sudden series of major life stressors	Impaired parent-infant bonding
Domestic violence in home	Young age, less than 3 years
Mental illness	Chronic illness, developmental delay or special needs
Substance abuse	Infant in care of non-biological caregiver
Lack of understanding of child behavior and emotional skills	Foster child
Attribution of malicious intent for age-appropriate behavior	Behavioral challenges

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care form the basis for patient care and approaching sensitive topics [8]. Physicians must approach each patient and family with kindness and compassion and provide adequate time for each person to narrate their concerns without pressure. Uncovering personal or family trauma offers an opportunity for deeper understanding of the struggles that might increase risk for maltreatment. The goal is to enhance relationships and improve caregiver capacity, expanding the ability for a parent or family to respond to stress in a supportive manner.

Neglect

Neglect is the failure of a parent or caregiver to provide for a child's basic needs and represents approximately 60% of reported maltreatment cases reported to child protective services [6]. In its most subtle form, this includes a lack of supervision and implementation of childproofing safeguards which increase the risk for accidental ingestions and unintentional injuries. Age-appropriate anticipatory guidance must be provided at each developmental stage, so parents and caregivers are prepared for the associated risks. Discussing the child's environment can uncover unforeseen hazards and provide an opportunity for education that nurtures parenting skills and mitigates hazard. Reviewing standardized handouts with the parent or caregiver such as the American Academy of Pediatrics' comprehensive Bright Futures handouts or The Injury Prevention Program (TIPP) Safety Sheets is an efficient way to incorporate anticipatory guidance into the outpatient well child visit. Individualizing parent or caregiver education is important, as there may be health literacy challenges that impede thorough understanding. Other forms of neglect include failure to provide for educational needs, failure to provide adequate food or shelter and medical neglect.

Medical Neglect

Medical neglect may present as a parent or caregiver not accessing medical care for a child when needed, not providing treatments that are deemed medically necessary or withholding medical treatment in the face of a life-threatening condition [9, 10]. Children without adequate medical care may present with untreated chronic conditions, lack of immunizations or injuries that have not healed properly.

Educational Neglect

Neglect of educational needs may be difficult to identify. Children who are frequently absent or do not attend school may not be recognized if the school district is under-resourced or overwhelmed, especially when facing situations such as natural disasters or a public health crisis. Children with special educational needs require extra support at home and school, and often fall behind when those resources are not provided. Some parents may find it difficult to advocate for their child and physicians may be a source of support or strength in providing suggestions for how and to whom they should voice concerns. Specific questions during a medical encounter about school performance, academic challenges, or behavioral issues may help to identify a child with educational needs so that the appropriate community resources can be provided.

Pediatric Undernutrition

In more serious forms of neglect, a child may exhibit growth failure and/or developmental delay due to insufficient caloric intake and inadequate nurturing. Pediatric undernutrition, formerly referred to as failure to thrive, is a clinical diagnosis typically defined as weight less than the fifth percentile or having declined down across two lines on the weight curve. Weight will decrease first as the body tries to preserve linear growth and head circumference, but these two measures will eventually falter when limited access to adequate calories is prolonged. While undernutrition includes both organic and non-organic causes, psychosocial factors account for about half of growth failure in infancy [11]. When undernutrition reaches a critical point, immune

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function may be impaired, putting the infant at risk for frequent, chronic or severe infections. The undernourished infant can become irritable or less engaging, which may disincentivize the parent or caregiver from caring for the child as attentively – further compounding the growth failure [11].

When a clinician is concerned about poor growth trends or failure to meet age-appropriate developmental milestones, a careful evaluation of growth patterns over time and a review of past medical history of the child including age of acquisition of developmental milestones, history of traumatic events or family stressors, detailed family medical and social history and knowledge of cultural norms should be considered. It is helpful to perform a comprehensive review of systems, with emphasis on gastrointestinal, genitourinary, neurological, cardiopulmonary, and endocrine systems. When reviewing the feeding history, physicians should pay attention to specific and concrete details of intake and output as detailed (Table 2). For organic causes of pediatric undernutrition, the central nervous system, musculoskeletal, cardiopulmonary, genetic, renal, and endocrine systems may be involved. Most of these disorders can be identified by characteristic physical features during the physical exam. The remainder typically reveal themselves on screening laboratory tests. If a psychiatric disease is identified during evaluation, attention to past trauma or abuse may help the patient on their road to recovery.

Early identification and effective intervention in cases of pediatric undernutrition result in better outcomes for the child and the family. Chronic undernutrition leads to cognitive impairments and developmental delay due to impaired brain growth and inadequate stimulation. This may not be fully reversible. Even once appropriate nutritional intake is resumed, the child may have residual difficulties such as behavioral problems in later childhood. Effective intervention should seek to assist the primary caregiver or parent, in a nonjudgmental and supportive manner, to understand the child's growth difficulties, nutritional needs, and obtain access to unmet medical, mental health, or social services to help achieve appropriate catch-up growth. A multidisciplinary team including a primary care physician, pediatric dietician, social worker, mental health professionals and others may be helpful to achieve such success [12].

Physical Abuse

Physical child abuse is defined as the intentional use of physical force against a child that results in physical injury. Physical abuse represents an estimated 19% of reported child abuse cases [11]. This can present in many ways, including contusions, fractures, burns, head trauma and other injuries. The evaluation of any suspicious injury requires careful assessment of the entire body for additional injuries, as well as those in various stages of healing. It is important to query the mechanism of injury and to further evaluate those situations in which the history and physical exam are inconsistent. The developmental stage of the child must also be considered when evaluating injuries, as this can provide information relevant to mechanism and likelihood of injury. Review of medical records for a history of frequent injuries may provide additional information that will aid in identification of child abuse. Table 3 outlines red flags for physical abuse of a child.

Table 2 Infant feeding history

Feeds offered	Type, volume, calories
Timing and context	Who is doing the feeding? Frequency, location in home, method, noise level, storage and preparation
Method	Breast – Time, frequency, latch, position, production, maternal fluid/diet intake Bottle – Type of formula, preparation, volume
Infant behavior	Interest, refusal, fussiness, sleepiness
Parental dietary beliefs	Concerns, fears, cultural considerations, source of information/support
Output	Voiding volume/frequency, stool volume/frequency, stool appearance

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Table 3 Red flags for physical child abuse

Current condition	Behavioral cues	Past medical history	Physical exam
Lack of history or unwitnessed injury	Delay in seeking care	Repetitive accidents or injuries	Fractures
Vague or incomplete story of injury	Parent-child interactions are strained, hostile or lack empathy	Poor adherence with appointments, delayed vaccines	Bruises to the head or neck, covered by clothing
History incompatible with severity of injury	Parent report of behavioral difficulties, crying prior to injury	Parent report of irritability, feeding or behavioral challenges	Burns
Story changes over time or conflicting account of injury	Parent labels child as clumsy or bad	Evidence that care is sought at multiple facilities over time	Multiple scars suggestive of prior injuries

When physical abuse is suspected, a comprehensive physical exam should be completed as soon as possible. While most physicians will not function as a forensic investigator, a complete history and physical are very important for ongoing evaluation and documentation of child abuse [13]. The physical examination should include vital signs, growth parameters including head circumference in infants, general appearance, a complete examination of the body surface examination, palpation of each bone and a complete examination that is focused on identification of injury and sequelae of prior injuries.

In children of all ages, it is important to consider the possibility of intraabdominal injury in those with substantial or suspicious soft tissue injuries. Useful laboratory evaluations include hepatic transaminases, complete blood count, coagulation studies and urinalysis. Sometimes a toxicology screen may be useful if an overdose or poisoning is suspected.

Patterns of Injury

When evaluating bruises and burns, the clinician should look for patterns that can provide clues to how the injury was sustained and document findings objectively [14]. Bruises are the most common presentation of physical abuse, and the pattern of the contusion often provides clues about the mechanism of injury (Table 4). For example, a bruise that has the appearance of a handprint might indicate a hard slap, while linear welts may indicate the child was struck with a belt. A small round burn might indicate intentional infliction with a lit cigarette. Burns that spare the space between toes and the palms of hands might indicate an intentional scalding.

Fractures

Significant contusions require further evaluation for fracture underlying the bruise. Because children under the age of two have more elasticity of connective tissue and bones, fractures cannot be excluded without radiography thus a skeletal survey may be indicated [15]. Children older than 5 years can usually provide a sufficient history of pain so screening imaging is not mandatory, but should be considered based on clinical findings. Between 2 and 5 years of age a clinician should consider other indicators of physical abuse and perform imaging if abuse is strongly suspected. The contents of the skeletal survey include individual films of the arms and hands, legs and feet, thorax, pelvis, spine and skull. Fractures that are highly specific for child abuse are those of the posterior ribs, sternum, scapula, spinous processes and metaphyseal fractures. Multiple fractures, those in various stages of healing, digital fractures and complex skull fractures are also suspicious for physical child abuse.

Abusive Head Trauma

Abusive head trauma is a leading cause of death in children under 5 years of age, with infants comprising 18% of cases [16]. Prevention education to

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Table 4 Injury patterns

Observation	Possible etiology
Round bruises in a fingertip pattern	Grabbing or gripping
3–4 small round bruises in linear pattern	Hit with a closed fist
Parallel, linear bruises with central sparing	Slapped
Circumferential bruises around body part	Ligature mark
Bruises adjacent to mouth	Gagged
Bruising or abrasions in arching pattern	Human bite
Bruising/abrasion in shape of object	Hit with object/implement
Petechiae of head/neck, subconjunctival hemorrhage	Strangulation

avoid shaken baby syndrome is essential for all parents and caregivers as it results in the death of about one in four babies affected. Shaken baby syndrome is a constellation of findings that include subdural hematomas, retinal hemorrhages, and posterior rib and metaphyseal fractures [13]. Many victims suffer from repeated episodes of abuse and the injuries can be severe with long-lasting impact such as macrocephaly due to posttraumatic hydrocephalus, chronic subdural hematoma or acute brain swelling and microcephaly secondary to posttraumatic cerebral atrophy. Other injuries include skull fractures, scalp hematoma, periorbital ecchymosis and subconjunctival hemorrhage [13]. These injuries may be difficult to detect, especially in small children, and may present as acute confusion, vomiting, lethargy, visual problems, hearing loss, idiopathic developmental delay, learning disabilities, behavioral problems, attention deficit and hyperactivity disorder, or a plateau in cognitive or physical development. Follow-up studies on victims of abusive head trauma indicate that one-third of victims have good neurological outcomes, one-third have moderate disability and the remaining third have severe disabilities [11]. Physical findings as seemingly innocuous as a ruptured tympanic membrane, but without evidence of recent infection, should raise suspicion for abuse.

Sexual Abuse

Sexual abuse of children is common, and those with disabilities, mental illness or chronic conditions are at greater risk. The CDC estimates that one in four girls and one in thirteen boys experience child sexual abuse [17], and that 91% of perpetrators are someone the child or the family knows [18]. Nine percent of reported child abuse cases involve sexual abuse [11]. When approaching a child or family when sexual abuse is suspected, it is important to recognize that any sexual activity where consent is not or cannot be given meets the definition for sexual abuse [19]. This includes any completed or attempted sexual act, sexual contact or exploitation of a child by an adult or caregiver [2]. Contact sexual abuse includes penetration, attempted penetration and sexual touching of any type. Noncontact sexual abuse includes acts of exposure, filming of a child in a sex act, sexual harassment or prostitution of a child.

The consequences of child sexual abuse may be extensive, potentially resulting in both physical and mental health consequences. While genital injuries are common, especially in young children they often heal quickly resulting in a lack of grossly identifiable injury pattern on physical examination. If extensive, these injuries can result in tears that require surgical repair, fistulas and incontinence. Sexually transmitted infections can result in infertility issues and chronic illnesses such as human immunodeficiency virus or hepatitis. Mental health sequelae include depression and posttraumatic stress disorder, as well as increased risks of substance abuse and suicidality. Children who have been sexually abused are more likely to engage in risky sexual behaviors, both in adolescence and adulthood, increasing their risk for sexually transmitted infections and unplanned pregnancies. They are also at increased risk for future violence and re-victimization.

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Sex Trafficking

Trafficking of children for sexual activities is increasingly reported in the United States and should be considered in a child or adolescent with an unusually high number of sexual partners or one who has knowledge of sexual acts that seem inappropriate for age and developmental stage. The Polaris Project reports a 19% increase in the identification of victims of all types of human trafficking from 2018 to 2019. Seventy-eight of those individuals for whom their age is known were determined to be minors at the time the trafficking began [20]. A disproportionate number of these victims are female, although male victims are also at risk, as are members of gender minority groups. Children are unable to legally provide consent for sex, so any commercial sex acts in which they are induced to participate are considered trafficking by United States federal law [19]. This includes prostitution, escort services, online advertisements to recruit buyers and pornographic photography or videography of a child.

Health services are a major point of contact for accessing assistance for victims of human trafficking [21]. A thorough and non-judgmental history is imperative that includes a confidential interview. As with other forms of abuse when one person is controlling another, queries should not be posed in the presence of the person who accompanies the child due to the risk of increased violence following the encounter. Common indicators for sex trafficking in the healthcare setting include an inconsistent or scripted history, a discrepancy between history and observations, severe trauma, malnutrition, or branding via tattoos or other means. Behavioral indicators include signs that the child is anxious or fearful. They may also display a depressed mood or self-harm behaviors. Substance abuse is common in victims of child sex trafficking and may be precede or follow the initiation of trafficking or sexual abuse. If a child appears much younger than stated age, it is prudent to check the Federal Bureau of Investigations missing persons database [22]. History should include queries about recruitment, threats and the extent of sexual activities the child was induced to participate or perform. If the child and clinician do not speak the same language, a trusted and reliable interpreter who is not connected to the suspected trafficking/abuse situation must be engaged. The physical examination should be targeted to address the child's specific concerns and should include evaluation for genital injury and sexually transmitted infections. Several protocols for the identification of human trafficking have been developed [23], but all begin with a trauma-informed approach to questions, assurance of confidentiality, patient comfort and assessment of safety.

Emotional Abuse

Emotional or psychological abuse is often harder to identify yet may cause more long-term consequences than physical abuse. Children who suffer emotional abuse such as rejection or withholding of love, belittling, humiliation or threats may present as an anxious or withdrawn child. School absences and a drop in school performance may be apparent in emotionally abused children [10]. While non-specific, the patterns of behavior that should alert the clinician to the possibility of emotional abuse include social withdrawal, anger or aggression, disordered eating, developmental delay or history of running away from home. Long-term exposure to emotional abuse may put a child at risk for depression and other mental health concerns.

Witness to Abuse

Children who witness violence are also prone to negative outcomes. This includes children exposed to intimate partner violence between parents or caregivers and witnessing death – especially if that person is a loved one. In some states, witnessing domestic violence in the home is considered child abuse and is reportable to child protective services. These traumatic childhood events often result in behavioral problems such as risky sexual behavior, violence toward peers, perpetration of sexual assault, and increased risk of becoming a runaway. Children who witness violence are more likely to

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develop mental health issues such as depression, anxiety disorders and substance abuse, and have a higher rate of suicide than their peers. Approximately 40% of children who witness intimate partner violence between their parents or caregivers are victims of physical abuse themselves [24].

Bullying

Childhood bullying is a common experience for children and adolescents, and an estimated 20% of children have been bullied at school [25]. Bullying is an unwanted, aggressive attack or intimidation that is intended to cause fear, distress or harm to the victim. Bullying can impact school performance and attendance and can increase the risk for self-harm, anxiety, depression, sleep disturbance, and feelings of isolation [26]. While there are no evidence-based screening tools specific to the identification of bullying, physicians can consider the use of the HEEADSSS tool as a screen to assess risk [27]. The American Academy of Pediatrics suggests clinicians introduce the concept of bullying to parents during the 6-year-old well child visit. Queries about school safety, academic performance, and relationships with other students and teachers will help to uncover problems with bullying at school [26].

Cyberbullying is becoming more prevalent with the widespread use of social media. The CDC estimates that 16% of children have been the victim of cyberbullying within the past year [25]. It may be difficult to identify since children may worry that their online activity will be restricted, thereby removing a source of social support [28]. Girls and sexual minorities are more likely to be victimized, and there are increasing reports of suicidality due to cyberbullying [29]. The Cyberbullying Research Center has developed a guide for healthcare providers [30].

Medical Child Abuse

While less common than other types of maltreatment, children are vulnerable to medical child abuse. Medical child abuse is defined as a child receiving unnecessary or potentially harmful medical care at the instigation of a parent or caregiver [9]. Factitious disorder imposed on another, formerly known as Munchausen syndrome by proxy, is a form of mental illness in which a caregiver seeks medical attention on behalf of a child who is not actually ill [31]. The Cleveland Clinic estimates one in twenty-five hundred child abuse cases are due to factitious disorder imposed on another [32]. It has been proposed that this number is likely an underestimate, since less severe cases of medical child abuse are unrecognized. In this rare form of abuse the parent or caregiver is willing to have the child undergo unnecessary testing, take medications, or induce illness or injury in the child to gain sympathy and attention. The onset of the child's illness is often gradual then escalates over time [31]. Diagnosis of medical child abuse is challenging as many parents or caregivers seek care from multiple clinicians. Clinicians can be misled into thinking the child actually has an illness, leading to further testing and referrals to subspecialists which perpetuates the abuse. When medical child abuse suspected, it is critical to access all historic medical records. An accurate diagnosis requires that the clinician maintain a healthy skepticism under certain circumstances. The prognosis of the child's physical, psychological, and social wellbeing can be poor if appropriate action is not taken [31].

Identification and Referral

Failure to consider child maltreatment as a possibility is a common barrier to identification [33]. Missed diagnosis of intentional injury, or failure to appreciate a pattern of repetitive injuries, is especially common when physicians are working with families who have sporadic or inconsistent access to healthcare. Family physicians may fear alienating parents or caregivers and may be wary of the stigma associated with child protective services involvement [34]. However, the process of identification and initial evaluation is well within the scope of practice of the family physician [35]. The healthcare provider who recognizes known or suspected child abuse serves as a link to

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the child welfare system and other community resources that can provide enhancement of recovery and promote resilience through identification of protective factors and elimination of risk factors. Validation of any disclosure, with reassurance that it isn't the clinician's response.

Referral to a child protective team for further evaluation of child abuse or neglect can be initiated by the family physician or child protective investigator, and the details included in the initial documentation of suspected or confirmed maltreatment are an important component of a formal investigation. The multi-disciplinary child protective team can provide several services including forensic interview and examination, psychological evaluation, child and family assessments and expert court testimony if needed. They frequently provide additional training for physicians who frequently encounter child maltreatment and those interested in participating in the child protection team.

Documentation and Reporting

Careful documentation of suspected or known child maltreatment is essential. This begins with a detailed description of the historical information that lays the foundation for the concern of abuse, neglect or exploitation, and includes a detailed description of disclosure when given. That information should be quoted exactly as provided by the child or parent/guardian, with the use of quotation marks where appropriate to document the specific utterances of those involved. Examination must be carefully recorded, including a detailed description of all injuries or signs of sexual abuse such as vaginal discharge or genital injuries. The physician should include photographs and/or drawings when appropriate. A brief safety assessment should be conducted to discern risk for both immediate and impending danger to the child [36]. Identification of protective factors offers an opportunity for families to enhance a child's response to stressful events or environments, augment parenting skills and well-being, and improve opportunities for connections and school-based interventions for children exposed to domestic violence [36].

Referrals to other care providers or community resources should be included in the documentation of the encounter, including a follow-up plan for ongoing care and evaluation. This record not only validates the concern, but also provides a resource for child protective services, court system and law enforcement when needed (Fig. 1). In some circumstances, a referral to a child advocacy center where a forensic evaluation can be completed is necessary. In most circumstances, it is not the role of the family physician to serve as an investigator for child abuse, but rather to link to services that are available and report as required by law. These issues are complex, and the information presented here should be augmented by knowledge of state laws and local resources.

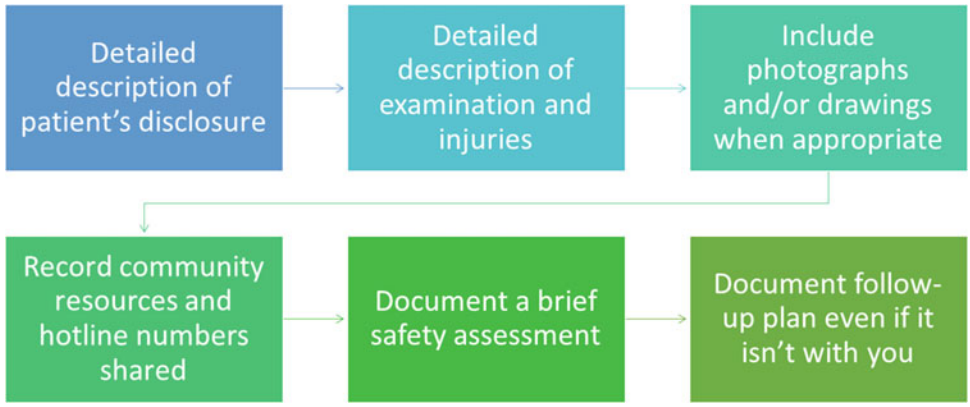


Fig. 1 Essential components of documentation for child maltreatment

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In the United States, The Federal Child Abuse Prevention and Treatment Act [19] requires that each State have provisions or procedures for requiring certain individuals to report known or suspected instances of child abuse and neglect. In most states and territories, physicians are mandatory reporters for child maltreatment, although in eighteen States and Puerto Rico, any person who suspects child abuse or neglect is required to report [37]. The specific laws, including the degree to which the reporting is protected as privileged communication, varies by state.

Summary

Child maltreatment is common, and physicians are mandatory reporters for suspected and known abuse, neglect, and exploitation. The American Academy of Pediatrics recommends clinician involvement in preventing child maltreatment and provides guidance on risk factors, protective factors, and clinical management [33]. The United States Preventive Services Task Force (USPSTF) concluded in 2018 that current evidence is insufficient to assess the balance of benefits and harms of primary care interventions to prevent child maltreatment, primarily due to the lack of clear benefit [38]. In 2019, the American Academy of Family Physicians supported the USPSTF recommendation regarding interventions to prevent child maltreatment, but reaffirmed in a policy statement that family physicians should be able to recognize the signs and symptoms of child abuse, be aware of community resources and reporting laws, and that they provide anticipatory guidance about child development, stressful stages, and appropriate techniques for discipline [35] (Table 5). Caring for victims of child maltreatment requires a multidisciplinary approach that should center on patient-identified needs including attention to education, psychological health of the child and family well-being.

Table 5 Interventions to prevent child maltreatment

Perform assessment of parental or caregiver well-being
Offer age-appropriate anticipatory guidance
Ensure parental access to material resources and food security
Improve stability of family unit
Provide tools to mitigate stressors within the family
Assess awareness of parental exposure to childhood trauma and abuse
Offer education for current and future developmental milestones
Assess and strengthen child's support system outside of family unit
Query exposure to violence
Provide education about substance use
Provide education about dating violence and sexual activity

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Intimate Partner Violence

28

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Intimate partner violence (IPV) is a serious but preventable form of violence that affects millions of Americans. Intimate partner violence, as defined by the CDC, is physical, sexual, or psychological harm by a current or former partner or spouse. It can occur among heterosexual or same-sex couples and in teen and elderly couples and does not require cohabitation or sexual intimacy [1].

Background

IPV is, at its core, about control and power. It is not merely tempers flaring and out-of-control behaviors perpetrated by individuals with anger management issues; it is an attempt by one member of a relationship to establish and systematically maintain control and power over the other.

Prevalence

While previous estimates of IPV have been inconsistent due to differing IPV definitions, survey strategies, and limited numbers of respondents, the large-scale National Intimate Partner and Sexual Violence Survey sought to clearly define IPV as well as capture a broad range of IPV behaviors. This has yielded some of the most comprehensive epidemiologic data on IPV to date. They identified four major subtypes of IPV:

1. Physical violence
2. Sexual violence
3. Stalking
4. Psychological aggression

According to this study, 36.4% or approximately 43.6 million American women have experienced physical violence, sexual violence, or stalking at some point in their lifetime. Among men, lifetime prevalence is 33.6% [1]. While the vast majority of male victims experienced primarily physical violence, the types of abuse suffered by females were distributed more evenly among physical violence, sexual violence, and stalking. Additionally, women experience more severe forms of IPV than men and are thus more likely to be severely injured, sexually assaulted, or murdered [2]. Also, about a third of all American women and men have been the victim of psychological aggression or emotional abuse by an intimate partner during their lifetime [1].

Intimate partner violence occurs across age, ethnicity, gender, and economic lines and among both heterosexual and homosexual couples. Nonetheless, there are both individual and social factors that affect the prevalence of IPV. Young age and low income have been found to be consistent demographic factors linked to men abusing their partners. Additional individual risk factors for becoming an abuser include low academic achievement, delinquency in adolescence, heavy alcohol use, depression, personality disorders, and witnessing or experiencing violence as a child [3].

There are also community risk factors for IPV. While IPV may be present in all socioeconomic groups, women living in poverty are disproportionately affected [3]. Poverty likely exerts multifactorial pressures on individuals and marriages, leading to frustration, hopelessness, marital discord, and higher IPV rates. How a community responds to IPV also affects its prevalence. Communities that punish abusers and those who offer victims sanctuary and support have the lowest rates of IPV. Cultural and societal factors may furthermore give rise to higher levels of violence among intimate partners. Women are more likely to be beaten by their husbands in societies where men have economic and decision-making control in the household, where divorce is uncommon, and where women commonly do not work outside of the home, and in places where individuals commonly use violence to resolve conflict [3].

Cycle of Abuse

In an abusive relationship, the partner being abused tends to fall into something known as the cycle of abuse. This cycle includes three phases, a tension-building phase, an abusive or explosion phase, and the apology phase, commonly known as the "honeymoon" period. Once initiated, the cycle repeats over and over again convincing

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the victim to stay in the relationship because the abuser apologizes, makes amends, and promises never to repeat the abusive behavior again. The victim is hopeful the abuser is capable of change, but the honeymoon period ends, tension builds, and more abuse occurs. Over time this cycle recurs faster and violence escalates.

Subtypes of IPV

Physical Violence

A range of violent behaviors are included in physical IPV. Acts of violence may include slapping, shoving, hair pulling, hitting, restraining, burning, choking, or harming with knife or gun. One in three American women has experienced some form of physical violence by an intimate partner in her lifetime [1]. Physical violence often escalates over time, placing the victim at an increasing risk for injury and death the longer she remains in a violent relationship.

Sexual Violence

Sexual violence may include rape (forced penetration or being made to penetrate someone else), sexual coercion, any kind of unwanted sexual contact. Nearly one out of five American women reports a completed or attempted rape by an intimate partner in her lifetime, and half have experienced any form of sexual violence by an intimate partner [1]. Sexually abused individuals report feelings of extreme guilt and embarrassment thus making it very difficult for them to disclose the abuse.

Stalking

Victimization by stalking may take many forms but can be defined as a pattern of harassing or threatening tactics used by a perpetrator that both is unwanted and causes fear or safety concerns for the victim. A perpetrator can stalk a victim in person, showing up at the victim's home, school, or workplace when unwanted. They may follow them, watch from a distance, track them using GPS, and even sneak into the victim's home, leaving frightening or threatening items or messages behind. Stalkers also commonly use phone calls, texts, emails, or messages via social media to send the victim unwanted or disturbing messages. Approximately 16% of women and 6% of men in the United States report that they have experienced stalking in their lifetime to the point of feeling very fearful or worried that he or she or a loved one would be harmed or killed [1].

Psychological Aggression

Acts of psychological aggression are varied, but all aim to exert control, erode the victim's self-esteem, instill fear, and garner power for the abuser over his or her partner. The most commonly reported behaviors include name-calling and use of insulting language, humiliation, angry behaviors that seem dangerous, and being kept track of by demanding to know one's whereabouts. In all, about a third of women and men report psychological abuse by an intimate partner during their lifetime [1]. Abusers may isolate their partners, not allowing the victim to leave home, drive, or use the telephone, keeping them from family or friends. They may make threats of violence toward the victim, their children, pets, or other family members. Abusers can destroy precious keepsakes, steal money, and hide medicine. When particularly desperate to maintain control in the relationship, especially when victims announce they are leaving, abusers may even threaten suicide, hoping to capitalize on their partner's guilt and convince them to stay.

Consequences of IPV

According to the World Health Organization, which has studied the pandemic of IPV in many countries worldwide, violence in a relationship has profound effects that extend far beyond the health and happiness of the victim. It has been tied to a large number of diverse negative health outcomes, some immediate and some long term.

Physical effects of IPV include cuts, bruises, and sprains that may result from hitting, punching, pushing, or thrown items. Broken bones, deep lacerations, organ damage, and permanent physical disability may result from more severe

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beatings or use of weapons [3]. While many victims present to a hospital emergency room for care of these injuries, others are forced to delay treatment or are denied treatment altogether.

In addition to the immediate physical injuries of IPV, there are many other associated health consequences with long-term effects. An IPV perpetrator may undermine his partner's ability to control her reproductive choices in order to maintain a position of power. Forced sex, unwillingness to use contraception, and interference with access to reproductive health services have been documented in many relationships with IPV. Thus, IPV is associated with unwanted pregnancy, sexually transmitted infections, miscarriages, repeat abortions, and poor pregnancy outcomes [4]. Chronic pain syndromes like fibromyalgia, neurological disorders including migraines, and gastrointestinal disorders are also increased [5].

Victims of IPV often develop long-term mental health problems as a result of the chronic trauma they endure. Individuals who are abused by their partners are more likely to suffer from depression, anxiety, phobias, sleep problems, eating disorders, psychosomatic disorders, substance abuse, and posttraumatic stress disorder (PTSD) [3]. Abused women are also at heightened risk for suicide and suicide attempts [3].

Homicide by an intimate partner is the most serious form of IPV. In most cases, the man in a relationship exhibits possessive, jealous behavior and obsesses over his partner. Tension and conflict build over time culminating in a major event that leads the man to act. The triggering event is often the woman's announcement that she is leaving. The time immediately after a woman leaves an abusive partner is the most dangerous for her and her children [6].

From 1980 through 2008, intimate partners committed 14% of all homicides in the United States. The total estimated number of intimate partner homicide victims was 2,340. In fact, 45% of all women and 5% of men who were murdered died at the hands of an intimate partner. Minorities are at higher risk with black women being more than four times more likely than white women to be killed by a current or former partner [7].

In one study, 82% of the men who killed their intimate partners were known to the authorities, either police or medical or mental health officials. Female victims of murder had almost always used a health-care agency in the months just prior to their deaths. These frequent contacts with helping agencies by both victims and perpetrators represent real opportunities for intervention and prevention of IPV homicide [8].

Even more disturbing are cases of familicide in which the abuser murders his intimate partner, their children, and then commits suicide. Thankfully, these cases are rare but nonetheless usually garner widespread media coverage. In almost all of these cases, the killer is a white, non-Hispanic man, has access to a gun, and has previous history of abuse [9].

Special Populations and Considerations

LGBTQ Couples

Lesbian, gay, bisexual, transsexual, and queer (LGBTQ) abuse victims have unique concerns and needs that are often misunderstood or ignored. Research indicates that individuals who self-identify as lesbian, gay, or bisexual have an equal or often higher prevalence of IPV compared to self-identified heterosexuals, with bisexual women being disproportionally impacted. Bisexual women reported significantly higher rates of physical violence, sexual violence, and stalking by an intimate partner (61% lifetime prevalence) than did their heterosexual or lesbian counterparts (35% and 44%, respectively) [10]. The same study found that 26% of gay men and 37% of bisexual men experienced IPV during their lifetime.

Transgendered individuals are at even higher risk for IPV. Approximately, 2/3 of all transgendered people report violence at home with more male-to-females (67%) than female-to-males (38%) reporting abuse. Most transgendered victims were particularly unlikely to report violence to police due to fear of revictimization [11].

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This fear of poly-victimization commonly exists across LGBTQ populations and refers to scenarios in which individuals are first abused by their intimate partners and later suffer more abuse at the hands of insensitive or homo-/trans-phobic law enforcement agents or health-care providers. This can compound their experience of trauma, can cause reluctance to seek out any kind of help, and requires the need for additional services to provide thorough support.

Abusive partners may employ tactics unique to the LGBTQ community. They may threaten to "out" their partner which may cause a profound impact on the victim's relationships with family, friends, or employers. Abusers may further block access to hormones or interfere with a transgendered individual's surgical treatments [11].

LGBTQ victims face additional challenges if they decide to reach out for help. As previously noted, they may meet resistance, ridicule, or frank discrimination from available helping agents. Even well-intentioned service providers may be incompetent regarding LGBTQ-specific language and culture. Many domestic violence shelters and services have been set up to exclusively aid and protect the stereotypical female victim from her male partner. Thus, there are many shelters where lesbian or trans-women are not welcome and even fewer shelters that can assist male victims.

Pregnant Women

Just as perpetrators may exert control over matters of contraception and sexual health, they may also seek to control the outcome of a pregnancy. Some women are forced to have abortions, while others who might desire termination are denied access by their partners. Between 3% and 9% of women experience abuse during pregnancy. Pregnant women who are young, single, members of a minority race or ethnicity, and living in poverty are at higher risk with IPV rates skyrocketing to nearly 50% during pregnancy [12].

Patterns of IPV for women may change when they are pregnant. Approximately 1/3 report pregnancy being a relatively protected period with less abuse, while the remaining 2/3 report either no change or an escalation of abuse [13].

IPV can lead to devastating consequences for both the mother and the developing infant. Many IPV victims face ongoing challenges in obtaining adequate care. In fact, victims of IPV are 30% more likely than their nonabused counterparts to receive inadequate prenatal care [14], missing more appointments, and experiencing late entry to care.

Aside from reduced medical care during pregnancy, abused women are more likely to have poor nutrition and inadequate weight gain. Certainly, concomitant maladaptive coping behaviors such as smoking and use of alcohol and illicit substances play a role in poor maternal health. These factors may lead to low birth weight and preterm labor, both of which are well-established risk factors for infant morbidity and mortality [12]. Also, the stress of experiencing abuse during pregnancy may alter a woman's hypothalamic-pituitary-adrenal axis. Animal models show that such stress in the perinatal period leads to heightened secretion of hormones, including corticotropin-releasing hormone, which may trigger preterm labor and can restrict uteroplacental perfusion [15, 16].

The most devastating consequences of IPV in pregnancy are fetal death and maternal homicide and suicide. IPV may contribute to spontaneous abortions and fetal loss as a result of blunt physical or severe sexual trauma to the mother by an abusive partner. Among pregnant women, 54.3% of suicides and 45.3% of homicides were associated with IPV [12].

Children

While child abuse is a topic covered in a separate chapter in this text, it is important to note that minors often suffer consequences when IPV is present in the home. Certainly, there can be an overlap of IPV and child abuse co-occurring with the abuser victimizing both partner and children. However, even when no direct physical harm befalls the children in the home, there is evidence that interparental violence leads to immediate and

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long-lasting negative outcomes for children witnessing it. As the level of verbal and physical violence escalates for a mother, her children suffer more conduct problems, more emotional problems, and develop lower levels of social functioning [17, 18]. It is also important to note that during adolescence, many children start to form their own intimate partner relationships. Without intervention and help, these children may start to accept and apply the same violent patterns they have learned at home in these relationships [19].

Teens

Teen dating violence is a widespread issue with 8% of high school students who dated someone in the past year reporting being hit, shoved, or physically hurt by a boyfriend or girlfriend [20]. Teens often think that certain behaviors like teasing, name-calling, and even physical fighting are playful, acceptable parts of a normal relationship. Over time, these behaviors may escalate to more serious forms of physical and sexual abuse and stalking. Among adult IPV victims, 22% of women and 17% of men report their first abusive relationships occurred during their teen years [1]. Programs aimed at the education of teens to promote healthy dating relationships may be a key to reducing violence in adulthood.

HIV

IPV can increase a woman's risk for acquiring human immunodeficiency virus (HIV). Higher rates of HIV in IPV victims may be due to forced sex with an infected partner or compromised negotiation of safe sex practices [21]. Additionally, IPV victims, constantly under threat of further abuse and in a state of chronic stress, often resort to maladaptive behaviors that further increase their risk for HIV [22, 23]. They report higher rates of intravenous drug use, treatment for other sexually transmitted infections, prostitution, and anal sex, all of which are known HIV risk factors [23]. Furthermore, among HIV-positive patients, associations have been found between IPV, poor HAART adherence, and faster CD4 cell count decline due to chronic stress and depression. This leads to disease progression and increased morbidity and mortality [24].

Immigrants

Immigrant women are more likely to be socially isolated and living in poverty, both risk factors for abuse. Unfortunately, there are numerous factors among immigrants that make it especially difficult to seek or obtain help. Identified barriers include threats of deportation by the abuser, language differences, worries about discriminatory or insensitive treatment, and a lack of familiarity with legal rights and the US social system [25, 26]. It is also recognized that some cultures have very strict and highly paternalistic views on marriage and gender roles. While health-care providers need to be culturally sensitive, violence and abuse are not excused by these cultural norms and need to be addressed for the safety and protection of all victims. Providers or community advocates who speak the victim's language and have an understanding of the victim's cultural practices are most adept at successfully uncovering IPV and offering appropriate services and support.

Disabled Persons

Acts of domestic and sexual violence are committed at higher rates against disabled individuals with twice as many disabled women experiencing nonconsensual sex by an intimate partner [11]. It is also important to note that the intersection of violence and disability may be glaringly apparent with some acquiring their disability as a result of IPV and then returning to live with and depend upon the abuser for aid [11]. Abusers are more likely to commit controlling acts upon partners with disabilities, such as limiting access to services and health care, withholding help with basic ADLs, and forced isolation. People with disabilities may lack access to shelters that are equipped to manage their medical as well as social needs.

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Deaf individuals or those with limited speech capabilities may face challenges in basic communication, while those with limited mobility may be unable to travel to places of aid due to environmental barriers such as lack of wheelchair ramps or elevators.

Public Health and Economic Burden

IPV is a clear public health and economic issue and the Affordable Care Act identifies IPV screening as a national health priority, alongside diabetes, HPV and cervical cancer, HIV, and other sexually transmitted infections [27].

With regard to business and economics, IPV reduces work productivity and leads to absenteeism. Nearly a quarter of employed women report that IPV has affected their work performance at some point in their careers [28]. There are also unfortunate instances in which domestic violence and stalking issues migrate out of the home and to a victim's place of employment. Companies must provide resources and support to these victims and take measures to ensure a safe work environment for all employees. Human resources staff should be trained to recognize potential signs of IPV, respond with support and advocacy, and, when appropriate, engage with law enforcement.

Even though IPV is generally thought of as a social and medical issue, it is possible to attach a true dollar cost to IPV in the United States. In a 1995 study, IPV against women alone cost $5.8 billion annually. Updated to 2003 dollars, costs would total over $8.3 billion per year [29]. A more recent 2018 study estimated the cost to be growing and would total $3.6 trillion dollars in lifetime medical costs and lost productivity [30].

Prevention

Although this type of violence exists in most countries and communities worldwide, interestingly there are some societies where IPV is virtually absent [3]. These societies can give advocates and victims hope that with proper organization of social relations, education, and programming, IPV can be successfully minimized.

The CDC asserts that IPV is preventable. Therefore, emphasis is being placed on interventions that prevent violence before it occurs. Many prevention programs target our nation's youth. Several are specifically aimed at promoting healthy dating relationships among adolescents and teens. These initiatives seem promising in that they address issues of respect, gender roles, and conflict resolution while promoting self-esteem and self-advocacy. Other programs target bystanders and witnesses of IPV, encouraging a more proactive role to support victims of violence [31]. Education of first responders is also necessary.

Screening

In order for any health screening initiative to be successful, physicians must recognize the importance of screening and make it a routine part of history taking. A meta-analysis of IPV screening practices showed that across medical specialties, screening rates were problematic. Only 1.3–12% of patients reported being screened for IPV by their primary care physicians. And for obstetricians and gynecologists, among the most active in advocating for IPV victims, only 10% of patients reported having been screened [32].

Most commonly, physicians stated that they did not screen because they either had a poor understanding of IPV, in general, they feared offending patients, they did not have adequate time to perform a screening, or they felt that there were inadequate resources and interventions for victims if IPV was uncovered [32].

Starting in 2013, the United States Preventive Services Task Force (USPSTF) recommended that clinicians screen women of childbearing age for IPV and provide or refer women who screened positive to intervention services. This recommendation is given a Grade B rating [5].

Physicians reluctant to screen based on time constraints should feel reassured that the screening tool most recommended by the USPSTF is quick

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and efficient to administer. With just four questions, the HITS instrument has high levels of sensitivity and specificity. It may be administered by the clinician verbally or by the patient in written form, and with the HITS acronym, it is simple to recall (**H**urts, **I**nsults, **T**hreaten, **S**cream) (Fig. 1).

Even with a convenient screening tool, a challenge worth noting in performing IPV screening of any kind is that patients are not likely to divulge violence in the presence of their abuser. Unfortunately, the batterer, in an effort to maintain control over the victim and to protect him- or herself from legal repercussions of abuse, often accompanies the victim to the emergency room and to primary care visits. He or she may hover and refuse to leave the patient alone and may insist on answering questions for the patient. These factors reinforce the necessity for taking the history in private, and astute physicians may need to employ some subterfuge in order to get the patient alone. Asking for a urine sample, for instance, is a simple way to separate the couple. While the abuser may think his partner may be just going to the restroom, the physician may instead bring the patient to another exam room to gather a more thorough violence history in private.

It is important to note that most patients will not spontaneously divulge IPV in their current or former relationships, yet want physicians to ask them about the topic in a supportive and confidential manner [34]. Incorporating an IPV history into routine history taking can identify IPV and build rapport between patient and physician. A sensitive and specific inquiry into IPV communicates to the patient that such issues are important to the provider. Even if a victim initially denies abuse, choosing to remain silent at the first inquiry, a seed of trust and support is planted, and he or she may open up at a future visit.

The HITS tool is a screening tool. It is not diagnostic, and should a patient screen positive, more detailed follow-up questioning is critical to better understand the full scope of abuse and immediate risk to the patient. When asking about IPV, providers need to provide a secure sense of confidentiality, offer support and make it clear that abuse is never the victim's fault, give judgment-free counsel, and offer to follow up. Like most items in the medical history, questions should begin open-ended (e.g., "tell me more about your home life" or "describe your relationship with your significant other") and then transition to more closed-ended, specific inquiries ("does your partner hit or push you?" or "have you been forced to have sex against your will?"). Because victims often do not

HITS Tool for Intimate Partner Violence Screening: Please read each of the following activities and fill in circle that best indicates the frequency with which you partner acts in the way depicted.

How often does your partner?	Never	Rarely	Sometimes	Fairly often	Frequently
1. Physically hurt you	O	O	O	O	O
2. Insult or talk down to you	O	O	O	O	O
3. Threaten you with harm	O	O	O	O	O
4. Scream or curse at you	O	O	O	O	O
Scoring	1	2	3	4	5

Each item is scored from 1-5. Thus, scores for this inventory range from 4-20.

A score of greater than 10 is considered positive.

Fig. 1 HITS tool for intimate partner violence screening. (HITS is copyrighted in 2003 by Kevin Sherin, MD, MPH and printed with permission) [33]

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talk about abuse unless specifically asked, clinicians should expect that open-ended questions may not always be high yield. If that is the case, the provider should be prepared to lead the conversation with a series of direct, closed-ended questions. Simple yes or no questions are far easier for reluctant patients to answer than having to verbalize all of the details of their abuse unprompted.

Management

As previously mentioned, physicians are often unaware of and disillusioned by possible interventions for IPV victims. In most American communities, there are services in place for abused individuals and their families, though services may vary and can be more difficult to access in some communities.

Resources

For help with assisting IPV victims, the National Domestic Violence Hotline is a good place to start. IPV victims, or health-care providers on their behalf, can call the 24-h hotline (800-799-SAFE (7233)) for help and support or visit the website (http://www.thehotline.org) for a listing of agencies nearby. It is also helpful to have a printed list of local agencies that the patient can discreetly take with her. Most local agencies are able to support victims in various ways. They may offer safe shelter, emotional support and counseling for all family members, free legal advice and advocacy, and access to local law enforcement if legal recourse is desired. Physicians should be able to either refer to such an agency or help give direct assistance if no convenient local agency exists. Health-care providers should not be forceful when making referrals or suggestions; rather, they need to allow their patients to decide how and when to proceed.

Safety Plans

While referrals and follow-up are necessary for long-term care and support, health-care providers must also suggest a safety plan for the victim to put into place immediately. Safety plans typically involve making preparations to escape acute danger and flee to a place of safety. Patients should be encouraged to pack a bag containing a few days of clothing for themselves and, when applicable, their children. The bag should also contain spare keys, copies of important legal documents (passports, birth certificates, and other identification), some money, and any necessary medication. Physicians should ask IPV victims to consider where they might go should they need to flee. Retreating to the home of a known family member or close friend may make it easy for the abuser to find the victim, so a relatively secret or unexpected location tends to be a safer option. If the victim has children old enough to understand, the safety plan should be discussed with them. They may also benefit from a secret safety word that could be used in front of the abuser to signify the need to leave and retreat to safety.

Documentation

Once recognized, IPV must be documented in the patient's chart. The victim may feel uneasy about the private details of her/his life being recorded, so it is important to reassure her/him that the records are confidential and may only be accessed with permission. Proper and thorough documentation of IPV is crucial as the medical record may need to be referenced to receive certain services or be utilized in legal proceedings. Historical components should be written precisely and chronologically. Statements in the medical record should be objective and, as much as possible, done using the patient's own words. Avoid medical jargon and, in paper charts, write with clear penmanship. Describe the patient's behavior and any injuries observed in detail. It is advisable to use drawings or photographs when possible and with permission to clarify the exact location and type of injuries present. Placing a coin or ruler next to an injury helps to notate size and scale in photographs, and, when possible, the patient's face should be visible. When able, take all photographs before treatments are administered.

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Reporting

Reporting of IPV is not as standardized and simple to understand as child abuse, for example, in which general mandatory reporting laws exist nationwide. Unlike a child or a disabled person who is unable to speak for and make decisions for him- or herself, mandatory reporting of IPV is problematic in many ways and thus is not a law in the majority of states. Mandatory IPV reporting undermines a victim's autonomy, interferes with confidentiality, and harms the rapport and trust built between the patient and physician.

Another reason that most states do not have mandatory reporting of IPV is that it has not been shown to improve outcomes. Calling the police or local agencies has been shown not to help but rather puts victims at increased danger due to retribution by their abuser.

IPV reporting laws vary from state to state, but generally fall into four categories:

1. States that require reporting of injuries caused by weapons
2. States that mandate reporting for injuries caused in violation of criminal laws, as a result of violence, or through nonaccidental means
3. States that specifically address reporting in domestic violence cases
4. States that have no general mandatory reporting laws

In addition to understanding your state-specific laws, certain IPV situations might require unique considerations. For instance, teen dating violence might meet criteria for mandated reporting under child abuse or statutory rape laws. IPV of a physically or mentally impaired adult or elder might also meet mandatory reporting requirements. IPV of a LGBTQ individual might be appropriately deemed a hate crime.

Even with an understanding of state laws, healthcare providers often recognize that implementation and policies can vary locally. Providers need to have knowledge of local reporting mandates and should consider contacting local IPV coalitions and law enforcement agencies to fully understand how the laws are specifically implemented in their particular municipalities [35].

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Sexual Assault

29

Lisa M. Johnson

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Introduction

Sexual assault is an act of violence and aggression and represents a complex problem with medical, psychological, and legal aspects. Because definitions vary among states, the term sexual assault is sometimes used interchangeably with rape. The Federal Bureau of Investigation's definition of rape recognizes that victims of rape and perpetrators may be of either gender and includes oral and anal penetration as well as penetration with an

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object. This definition also includes instances in which the victim is incapable of giving consent because of temporary or permanent mental or physical incapacity (including due to the influence of drugs or alcohol) or because of age. Physical resistance is not required on the part of the victim to demonstrate lack of consent [1, 2].

Occurrence

In a nationally representative survey of adults, nearly 1 in 5 (18.3%) women and 1 in 71 men (1.4%) reported experiencing rape at some time in their lives. There is a lifetime prevalence of rape of 13% for women and 6% of men. 42.2% of female rape victims were first raped before age 18 years. Among female rape victims, perpetrators were reported to be intimate partners (51.1%), family members (12.5%), acquaintances (40.8%), and strangers (13.8%). Among adult women surveyed in 2010, 26.9% of American Indian/Alaska Natives, 22% of non-Hispanic blacks, 18.8% of non-Hispanic whites, 14.6% of Hispanics, and 35.5% of multiracial women experienced an attempted or a completed rape at some time in their lives. Among male rape victims, perpetrators were reported to be acquaintances (52.4%) and strangers (15.1%) [3].

Impact

The potential short-term and long-term health effects of sexual violence are well established. Potential short-term effects include injury, sexually transmitted diseases, and pregnancy. Long-term effects include somatic complaints, psychiatric disorders, and such health risk behaviors as substance abuse, suicidal ideation, and chronic physical health problems.

Studies also report impaired physical, sexual, and psychosocial functioning, decreased quality of life, increased risk for re-victimization, and problems with access and use of health-care services [4]. Female victims of sexual assault are more likely to engage in risky health behaviors such as hazardous alcohol use and use of sexual behavior to regulate negative affect [5].

Female Victims

Women aged 16–24 years are four times more likely to be assaulted than women of any other age [6]. Among college women, sexual assault is a significant public health problem. 11–20% report that they experienced completed sexual assault perpetrated by threat or force, or the incident occurred when they were incapable of consenting. Female victims in underrepresented minority groups may experience more PTSD symptomatology and may be more likely to believe that their community blames them for the assault [7]. Because the incidence of sexual violence in some racial and ethnic minority populations is higher than many white populations, it is important to understand the role played by health and community disparities when planning emergency care interventions and for preventing adverse health outcomes [4].

Female veterans experience high rates of sexual assault during their service in the military. They are eligible to receive lifetime care at any Veterans Health administration facility for health problems related to military sexual assault [8].

Male Victims

Prevalence rates of male sexual assault are difficult to calculate, as few victims report their assault to the police or medical services [9]. It is estimated that 1 in 71 or 1.4% of men report experiencing rape at some point in their lives [3]. While sexual assault of males occurs less frequently than females, it is not limited to all male populations such as jails or prisons. While most perpetrators of male sexual assault are male, women are perpetrators too. A comparison of data between male and female victims shows that both groups are assaulted by strangers at the same rate, but males are more likely to have more than one assailant. A higher proportion of victims are identified as gay, bisexual, or having consensual sex with men.

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Many assaults of men involve anal rape. Men are more likely to be assaulted by acquaintances. The motivations of their assailants include sexual gratification, conflicted feelings about sexual orientation, humiliation of the victim, and exercising power and control [10].

Intimate Partner Violence

An intimate partner is a current or former spouse, an opposite or same sex cohabitating partner, or a boyfriend, girlfriend, or date. Intimate partner violence entails physical, sexual, or psychological harm by a current or intimate partner, and it affects millions of people per year. Intimate partner violence is commonly associated with sexual assault. Sexual assault that occurs within an intimate partner relationship has been shown to result in an increase in PTSD symptomatology [11]. It is commonly believed that sexual assault is more traumatic when committed by an unknown assailant; however, sexual assault in marriage or dating relationships has been found to be equally detrimental to women's physical and mental health [12, 13].

The Family Physicians' Role

In 2011, the American College of Obstetricians and Gynecologists recommended that health-care providers routinely screen all women for a history of sexual assault, paying particular attention to those who report pelvic pain, dysmenorrhea, or sexual dysfunction. Prevention of long-term physical and mental consequences can be prevented by early identification of victims [1].

The physician conducting an evidentiary evaluation of a sexual assault victim must comply with state and local statutory or policy requirements involving the use of evidence gathering kits. If a sexual assault victim communicates with the physician's office, she/he should be encouraged to immediately go to a medical facility, not to bathe, change her clothing douche, urinate, defecate, wash out her mouth, clean her fingernails, smoke, eat, or drink [1, 14].

The time limits for evidence collection depend on the jurisdiction and range from 72 to 120 h. The evaluation and treatment of sexual assault victims are time-intensive and should optimally be provided by a team that includes an emergency physician or other medical provider overseeing care and treating injuries, a trained sexual assault examiner, and a social worker or rape crisis counselor who has expertise in acute reactions to rape and can assist in offering support, describing options, and explaining the hospital process. Physicians should understand that it is not their responsibility to determine whether a sexual assault has occurred since such a determination will be made through the legal system [15].

Care of the Victim

When a history of sexual assault is obtained, the clinician may expect that recounting of the incident and various health-care procedures such as pelvic or rectal exams may trigger anxiety reactions [1]. A carefully recorded history should be obtained from the victim. The history should include general medical history, sexual history, and OB/GYN conditions, including current pregnancy or risk of pregnancy. The health-care provider should document the victim's emotional condition.

General body trauma is more frequent than genital trauma in up to two thirds of rape victims who present to the ED [15, 16]. Injuries may include blunt or penetrating injuries to the head, face, torso, or extremities as well as defensive injuries such as lacerations, abrasions, or bruises.

The collection of evidence is a multistep process that can take several hours and is optimally performed by specially trained personnel. The purpose is to collect and record evidence including DNA to support the victim's report of the assault. Evidence collection requires the patient's consent at each step, and the examiner should explain each step of the process to the victim. A detailed examination of the entire body should be performed with injuries being photographed or drawn accompanied by a written description and location of each. Sheets in which the victim is

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transported should be preserved and folded. Before a Foley catheter is placed, evidence that may contain DNA can be collected from the vagina or penis. Standardized evidence collection kits contain forms for documentation to assist examiners.

Because a meticulous pelvic examination is required, anesthesia may be required to enable patient cooperation. With witnesses present (and named in the record), inspect the perineum and vulva for abrasions, ecchymoses, and lacerations. Over 90% of victims will have trauma at one or more of four locations: posterior fourchette, labia minora, hymen, and fossa navicularis. Tears occur most frequently on the posterior fourchette and fossa. Abrasions are usually seen on the labia and ecchymoses are most often seen on the hymen.

An alternate light source (ultraviolet illumination) should be used to check the patient and her clothing for semen. Positive areas should be blotted with saline-moistened filter paper, labeled, and packaged separately. Pubic hair should be combed, and both the comb and material obtained should be packaged together. Pubic hair cuttings should be obtained, as well as scrapings from under the fingernails.

Each specimen should be packaged separately and labeled with source, patient's name, and date. All assembled items should be sealed individually and then sealed together in a large container to verify that they were unaltered during transfer to the law enforcement agency. The person who accepts the evidence should sign for the material, and this transfer should become part of the chart. In brief, the record should reflect the chain of evidence.

The vaginal speculum should be moistened with saline only, and careful inspection of the vagina should be performed. Saline-moistened cotton swabs may be used to obtain fluid from the vaginal pool and the endocervix and placed in labeled, corked sterile glass tubes for culture for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. The same fluid should be applied to glass slides and air-dried but not fixed. Next, deposit 2 mL of saline in the vaginal vault, and with aspiration, search for motile sperm (often motile even 4–6 h after ejaculation). If the mouth or anus was penetrated, similar specimens should be obtained. Blood should be drawn for VDRL and blood type. HIV as well as hepatitis (B and C) testing at this time and later should be offered. Proper labeling of all samples is essential [17].

A pregnancy test is advisable if the patient may have become pregnant during the assault. The risk of pregnancy after rape is approximately 5%. Emergency contraception (EC) should be provided. Progestin only EC (1.5 mg of levonorgestrel) administered as a one-time dose within 120 h after unprotected intercourse has been shown to be 98.5% effective in preventing pregnancy. The best efficacy is within 72 h of the sexual assault [15].

There are long-term health consequences that are associated with sexual assault such as increases in somatic symptoms, diminished levels of function, alterations in perceptions of health, and decreased quality of life. Some women may present with complaints of chronic pelvic pain, dysmenorrhea, or sexual dysfunction without disclosing a history of sexual assault [1].

STI Prevention

All patients should be offered prophylaxis for STIs [18] (Table 1). The most common sexually transmitted infections reported in sexual assault victims include trichomoniasis, gonorrhea, and *Chlamydia trachomatis* [19]. The HIV status of assailants is usually unknown and tends to be of great concern to the victim. And although it is infrequent, cases of HIV transmission following sexual assault have been described [20, 21]. Genital or rectal trauma, multiple traumatic sites involving lacerations, or deep abrasions and the presence of preexisting genital infection or ulcers in the victim increase the risk of HIV transmission [22]. Health-care providers should carefully consider several factors when deciding to recommend the initiation of postexposure prophylaxis (PEP) after sexual assault, such as whether or not a significant exposure has occurred during the assault, knowledge of the HIV status of the alleged assailant, and whether the victim is willing to complete the PEP regimen. Clinicians should

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Table 1 STI prophylaxis after sexual assault

Cefixime 400 mg orally in a single dose
or
Ceftriaxone 250 mg IM in a single dose
plus
Azithromycin 1 g orally in a single dose
or
Doxycycline 100 mg orally twice a day for 7 days
Plus
Metronidazole 2 g orally in a single dose
Postexposure hepatitis B vaccine (without HBIG) – at the time of the initial exam, at 1–2 months and at 4–6 months after the first dose
If the survivor appears to be at risk for HIV transmission (start within 72 h of assault) – lab work prior to start: pregnancy test, HIV test, CBC, and CMP
Tenofovir 300 mg orally daily + emtricitabine 200 mg PO daily
Plus
Raltegravir 400 mg orally twice daily
or
Dolutegravir 50 mg PO daily for 28 days

recommend HIV PEP when significant exposure may have occurred. PEP should also be offered in cases of bites that result in visible bleeding. PEP should be started as soon as possible, ideally within 2 h of the assault. Some guidelines restrict initiation of PEP to 36 h after the exposure as it is noted that there is diminished efficacy of the regimen by delaying its initiation. The patient's HIV status should be tested within 72 h of the initial assault and then repeated at 3 months and 6 months. The health-care provider should provide HIV risk reduction and primary prevention counseling whether or not PEP was initiated [23]. HBIG should be administered if the assailant is known to be hepatitis B positive; otherwise, active immunization alone for hepatitis B may be considered.

Emotional Reactions and Psychological Sequelae

After the assault, a rape trauma syndrome often occurs. The initial or disorganization phase may last days to weeks. The victim may experience physical reactions such as generalized pain, eating and sleeping disturbances, and emotional reactions such as anger, fear, anxiety, guilt humiliation, embarrassment, self-blame, and mood swings. The second or delayed phase is characterized by flashbacks, nightmares, and phobias as well as somatic and gynecologic symptoms. This phase often occurs in the weeks and months after the event [1, 24].

Longitudinal data indicate that sexual assault survivors are at increased lifetime risk for posttraumatic stress disorder (PTSD) 30%, major depression (30%), and contemplation of suicide (33%) or an actual attempt (13%). Risk factors for PTSD after rape include previous depression, alcohol abuse, and increase severity of injury during the assault [15, 25]. Health-care providers should enlist the input of social workers or rape crisis counselors to help evaluate the patient's immediate and future emotional needs and formulate a plan for safety after the patient is discharged home.

Follow-Up

Sexual assault victims should be referred for both medical follow-up (testing for pregnancy, HIV, and hepatitis) and psychological or psychiatric support. Rape crisis centers can provide ongoing support, free confidential counseling, and legal services. Some states require mandatory reporting of rape (with identifying information either included or removed) or weapon-related injuries in a competent adult. All jurisdictions require reporting the assault of a child or an elderly or disabled person.

Prevention

Prevention of sexual assault is a societal issue. Programs that are effective address public attitudes about relationships and sexuality and teach conflict resolution skills. Teaching women life skills may decrease their vulnerability to sexual assault or re-victimization. Support and safety programs, transportation policies and procedures, campus and community safety programs, and

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crime prevention programs have all been shown to decrease the incidence of sexual assault.

Recognizing that a sexual assault has occurred and providing the victim effective care represents primary prevention of re-victimization and secondary prevention for the victim. Prosecution rates are improved when care is provided by victims' advocates, as well as by physicians, and other health-care professionals particularly nurses who have been trained in programs such as Sexual Assault Nurse Examiners can provide accurate collection and documentation of forensic evidence [26, 27].

Conclusion

Sexual assault is an act of aggression by the powerful on the less powerful. Although both women and men can be sexually assaulted, women are at greatest risk. Family physicians must be prepared to recognize and treat victims of sexual assault. Treatment of the woman who has been sexually assaulted should address legal, medical, and psychosocial aspects of care and should be coordinated with law enforcement, victims' advocates, psychological support, and other trained medical personnel [25, 27, 28].

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Part VII

Behavioral and Psychiatric Problems

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Managing Mentally Ill Patients in Primary Care

30

Laeth S. Nasir

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General Principles

Definition/Background

Because mental illness is so common and may cause as much or more disability than many chronic medical illnesses, psychological assessment is integral to the evaluation of each patient in the Family Medicine paradigm.

Most perturbations in the psychological state of patients presenting to the attention of the family

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physician are, like most physical illnesses, transient or minimal and not likely to significantly impact health. Sometimes these issues can be more pervasive; many of these are related to the patients' social and existential milieu. Finally, there are patients who display symptom clusters of a quality, severity, and chronicity most consistent with classically described psychiatric conditions. Differentiating between these groups of patients may be difficult. Symptoms may fluctuate significantly over time, so at times they meet criteria for a diagnosis of a psychiatric disorder, and at other times, they do not. Longitudinal follow-up may be helpful to assess the importance of symptoms in a given patients' life.

While contemporary psychiatric classifications of illness represent the pinnacle of our current understanding of the neurobiological basis of many psychiatric conditions, they often do not comport with the patients' own lived experience, do not fit easily into the realities of the primary care setting, and may not be very successful in bringing about satisfactory patient-centered outcomes [1–3]. Assumptions that the psychiatric populations seen in primary care and tertiary care are identical may result in a "category fallacy" when using standard criterion-based diagnosis systems used in subspecialty care [4]. While it is important for the physician to try to focus on the assessment of behaviors that are observable, measureable, and therefore reproducible, this unavoidably reductionist approach excludes or discounts many factors that might be important to the patient and may risk medicalizing normal human experience.

It has been suggested that an alternate, pragmatic system of classification of patients with mental health problems be developed to better categorize the range of disorders seen in primary care [5].

Regarding the treatment of mental health issues, it is increasingly recognized that measures and outcomes that are important to clinicians and health systems may not always be the yardsticks that are meaningful to patients. In-depth studies of patient outcomes have identified that some aspects of the organization of mental health practice may actually interfere with a patients' ability to fully recover from mental illness. Individuals with chronic mental health issues often end up living in "virtual institutions" where all aspects of their identity are directly linked to the mental illness through their social network and housing, for example. Ultimately, mental illness, and its associated dysfunction, becomes inextricably linked to their sense of self, which can be a barrier to improvement [6].

With this fact in mind, many health systems worldwide are rethinking and overhauling their approaches to the management of psychiatric illness. The "recovery" movement recognizes that many individuals with chronic mental illness will never achieve "normality." Instead, aiming for reintegration of these patients into society in order that they might attain a meaningful and fulfilling life becomes an important focus.

When encountering a possible mental health problem, the family physician often faces a series of very challenging tasks. The multidimensionality of undifferentiated patient presentations often makes the assessment of these patients highly complex. In addition, the ability of the physician to articulate the problem in a way that makes sense to the patient and then to negotiate a narrative that provides an opportunity to use the resources available to develop solutions to the patients' problems is one of the keys to providing the highest quality mental health care in the primary care setting. An overreliance on reductionistic models, based on rigid criteria, may not be helpful in many cases and may be associated with high rates of nonadherence, ineffective treatment, and premature termination of care [7].

Epidemiology

Mental health problems are very common. National surveys estimate that in 2012, 4% of adults in the United States suffered from a mental illness that significantly affected day-to-day living, and in that same year, 18.6% of all adults suffered from some kind of mental disorder classifiable according to the DSM [8]. Data from both the United States and international sources reveal that the majority of patients with a mental health problem never come to medical attention, instead seeking care through informal channels that may

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include friends, family, and alternative practitioners. Of those who do seek medical attention, only a fraction are seen by professionals specializing in mental health care [9, 10]. This means that most people with mental health issues who go to a doctor present to the primary care physician and will never interact with a mental health professional. Additionally, many patients who do ultimately receive mental health treatment from a subspecialist subsequently drop out of care [11]. Overall, it is estimated that at least 90% of medical mental health-care worldwide is delivered by primary care physicians [5].

High levels of morbidity and mortality are observed among patients with serious mental health issues, and these are a particular cause of concern for the family physician. Several studies have documented significant reductions in life expectancy among patients with chronic mental illness. This excess mortality is thought to be due to the behavioral clustering associated with these conditions that include smoking, substance abuse, poor diet, and lack of exercise [12–14]. Other data suggest that disruptions in neurohormonal systems caused by mental illness may also contribute to morbidity [15]. In addition, long-term effects of certain psychiatric medications may increase risks of obesity, metabolic syndrome, and its attendant conditions [16]. The monitoring, prevention, and treatment of these conditions are often overlooked in caring for these patients. A review of interventions to reduce health-risk behaviors and medical conditions among patients with schizophrenia and bipolar disorders found that there was good evidence to support behavioral interventions for weight loss, and the use of varenicline and bupropion for smoking cessation [17]. However, only a few studies have been carried out in patients with psychiatric illness, particularly in primary care settings, and more work is needed to explore the effectiveness of interventions for prevention in these populations [18].

Approach to the Patient

Patients presenting to primary care with mental health problems typically differ in important ways from the ones seeking help from subspecialty psychiatric care. In the subspecialty psychiatric setting, virtually all patients have accepted a psychiatric dimension to their illness and so volunteer emotional symptoms as a matter of course. In contrast, in the primary care setting, patients are much less likely to relate affective or behavioral symptoms, instead focusing on a combination of somatic complaints and social factors. Very often, they do not perceive the emotional and psychiatric aspects of their condition. The willingness of individuals to consider a psychiatric dimension of their illness varies widely and may be influenced by among other things, the feelings of disempowerment and stigma associated with mental illness [19]. In addition, cultural, social, or personality characteristics particular to individuals or groups of patients may discourage recognition or acceptance of a psychiatric diagnosis. Also, the illness itself may interfere with insight. This may result in unconscious or conscious attempts to rationalize, discount, conceal, or disguise symptoms that they may perceive to be "psychiatric" in nature. Failure of the physician to ferret out the condition then provides the patient with "evidence" that the problem is a (more acceptable) physical one. It is not unusual to encounter patients who are so resistant to the idea of a psychiatric component to their illness that they demand further extensive testing to detect unlikely physical illnesses, refuse, or (more commonly) fail to adhere to treatment, or simply find a different, and hopefully more malleable practitioner.

This dynamic highlights the central role that establishing trust and the development of a common understanding between physician and patient has in improving rates of treatment of mental health problems [20]. Trust is usually developed through ongoing and bidirectional communication that gives coherence to the patients' own experience, allows them to develop an acceptable context in which to place their illness and ideally to develop a narrative of coping or healing.

Among those who are reluctant to consider a mental health explanation for their symptoms, rolling with the patients' resistance, "planting a seed," and allowing them to consider the issue at leisure will often result in their being much more amenable to consideration of an emotional or psychiatric dimension of their condition in future visits.

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One approach that has been quite successful for this author, when faced by resistance in the face of a likely psychiatric diagnosis is to tell the patient, for example, "I'm not certain what is causing this condition" and provide a differential diagnosis that includes both possible physical causes and psychiatric condition(s). "What I would like you to do is over the next week or two is to have you monitor and record your symptoms and also record what is going on during the day, including any issues that result in stress to see whether they affect your symptoms."

Diagnosis

Screening for mental health problems is frequently carried out in the primary care setting in high-income Western countries. Using standardized instruments for the diagnosis of depression, for example, improves the detection rate of this condition; in the absence of screening, only about 50% of cases are detected [21]. Screening may also allow patients another avenue by which psychological discomfort can be articulated and brought to the attention of the physician. However, controversy exists regarding the costs and benefits of screening for many mental health conditions in primary care and may depend on whether resources are available to ensure that the problem can be treated effectively if it is discovered [22]. However, little evidence is available to assess the efficacy or acceptability of this kind of screening in many cultures.

The detection of mental health issues in the primary care setting depends largely on characteristics of both the patient and the physician. Although the well-documented lack of detection and treatment of mental health issues in primary care is widely assumed to result solely from a knowledge deficit on the part of physicians, the widespread ineffectiveness of educational interventions suggests that there are a number of more important issues that result in the outcomes observed [5]. In most general medical settings, there are a number of barriers that may interfere in making a diagnosis of a mental health condition. These include the poor fit of psychiatric classification systems in primary care as mentioned above, variations in the training or other characteristics of the physician, the undifferentiated nature of many mental health presentations, patient characteristics, and systems barriers.

Since most current workflows in primary care are not designed to deliver mental health care in a way that differs paradigmatically from the care of most physical disorders, the system in which the physician works is often the major barrier to addressing and treating these problems. Time pressure is one of the most commonly cited of these. It is well recognized that the number of complaints presented by a patient in the primary care setting is directly proportional to the nonrecognition of mental health problems. One solution which is becoming more popular is the development of "colocated mental health services" in which detection of a mental health problem results in the patient being comanaged with a mental health professional who has the time and specialized training to focus solely on the mental health issue that is suspected or identified.

The availability of appropriate triage options or medications is another barrier. Many physicians may correctly surmise that there is little to be gained by making the diagnosis of a stigmatizing psychiatric condition if it is unlikely that the patient is going to receive successful treatment for it, or if the perceived social costs to the patient of making a diagnosis will outweigh the benefit of treatment [23]. In some countries, psychiatric medications may not be available in the primary care setting, and cost may be another limiting factor in many settings. Lack of availability of counseling services also may be a problem. Other barriers to the treatment of mental health problems in primary care have been recognized, including one study that found an association between lower rates of recognition of a mental health problem and the use of electronic health records [24].

These systemic barriers may lead some physicians to avoid "the can of worms" posed by a potential mental health issue. This may lead them to implicitly collude with the patient by accepting the validity of the patients' somatized

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"ticket of admission" to the doctor, and, instead of addressing it, to ignore it or to defer addressing the problem.

History

A unique characteristic of primary care is the longitudinal relationship shared by the physician, patient, the family, and ideally the community. This has a number of advantages that include the ability to observe symptoms at intervals, the time to develop trust and a shared understanding and narrative about the condition, and the ability to contextualize both the diagnosis and treatment. A longitudinal relationship also may have the disadvantage of "foreknowledge" that may result in the clinician discounting apparently new discordant information or observations that arise during the course of a familiar relationship.

Review of the patients' past medical record, when it is available, is often very helpful. It is quite common for patients with undiagnosed behavioral problems to make frequent visits to various practitioners and care settings with vague or recurrent mild or undiagnosed illnesses. However, it should be noted that at least one study has found that the majority of patients with undiagnosed physical symptoms presenting to primary care do not have a mental disorder [25]. A thorough evaluation of the record may reveal a previous clinicians' recorded suspicion of a mental health problem, though follow-up may not have occurred. Alternatively, prescribing patterns of previous physicians – such as the frequent prescription of benzodiazepines – may suggest that they had considered the possibility of a mental health condition that they may not have directly addressed or recorded.

Patients presenting to the physician with a previously diagnosed mental health condition are also commonly seen. Not infrequently, patient records are unavailable or may be inadequate. While many patients may have a good understanding of their illness and can recount their history and treatments, others may suffer from enough impairment or deficient communication skills that it is difficult to get a good idea of the patients' past history and what previous treatments have been attempted. Others may minimize or conceal their history to avoid memories of a painful chapter in their lives or to avoid a possible negative judgment by the physician. At times, it is only after a trusting relationship has developed that the history of a mental health problem emerges.

A careful history around current and past use of substances is warranted. Substance abuse is often comorbid with other mental health issues and may be even more difficult to uncover than the associated psychiatric condition. Comorbidity of mental health and substance use disorders complicates the course and worsens the prognosis of both disorders [26]. Patients with a past history of substance abuse are prone to relapse in the face of exacerbations in their mental health condition.

Mental health conditions are often brought to the attention of the physician by family members or other concerned individuals in the patients' social environment. The role of collateral informants is often invaluable in determining prior functioning, premorbid personality traits, and family history. These may provide critical clues to the diagnosis and an assessment of the problems' severity. Further, friends or family members may help to negotiate appropriate treatments with the patient. Finally, understanding the support and social capital that the patient enjoys may be important in assessing prognosis.

Physical Examination

Findings on the general physical examination are very important. Psychiatric symptoms can be due to many conditions – ranging from the side effects of over-the-counter supplements to genetic, metabolic, neurologic, immunologic, and malignant disorders. Even after the diagnosis of a primary psychiatric disorder is made, the physician must keep an open mind about the presence of an underlying physical illness. A slowly progressive occult illness may initially manifest with a mental health problem and remain hidden for some time despite negative initial evaluations for organic disease. The old adage that even people who

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somaticize develop a "serious" physical illness eventually must also be kept in mind.

Dress, mannerisms, affect, and hygiene may all provide clues to the patients' illness, background, or the image that they want to project to the examiner. Subtle abnormalities in cognition or mental status might point to the diagnosis of a neurological condition such as frontotemporal dementia or psychosis. Many chronic illnesses, such as Parkinson's chronic lung disease and patients with cardiovascular or cerebrovascular disease, are associated with very high rates of mental health diagnoses, particularly depression. The clinician should maintain a high index of suspicion for comorbidity in these patients. The association of neuroleptic medications with development of the metabolic syndrome may lead to obesity, hypertension, and acanthosis nigricans. Other stigmata such as tardive dyskinesia, jaundice, gingival hypertrophy, petechiae, or pallor due to the adverse effects of medications may be apparent on physical examination.

Laboratory and Imaging

It is always correct to acknowledge that any investigations should be guided by the results of the history and physical exam. When making a diagnosis of a psychiatric condition in a patient with an unrevealing history and physical examination, this author will often obtain baseline laboratory testing to include a complete blood count, comprehensive metabolic panel, and thyroid-stimulating hormone, in order to screen for occult conditions which may be difficult to detect with less invasive measures.

Many patients with serious mental illness may have a long history of chronic medical conditions, abuse, and social adversity; the physician should be alert for associated illnesses, such as sexually transmitted or blood borne infections, and chronic infections such as tuberculosis. Additionally, routine health maintenance measures, such as lipid measurements and mammograms, while sometimes requiring additional diligence to ensure that these are adhered to by the patient, should not be neglected. In addition, patients taking certain medications chronically for psychiatric problems may require periodic laboratory testing to detect toxicity, and the family physician should be familiar with routine testing recommendations for these medications.

Differential Diagnosis

As mentioned above, the differential diagnosis of psychiatric conditions is vast; psychiatric symptoms may be a manifestation of virtually every category of illness including malignancies, rheumatological conditions, toxic ingestions, infections, injuries, and endocrinopathies.

Particularly common issues in primary care that should be specifically considered include occult substance abuse, sleep apnea, and social difficulties such as abuse or family stress. The family physician must maintain a reasonable level of suspicion for an underlying physical or social condition while maintaining equanimity in the face of some level of uncertainty.

Treatment

In the past few years, the development of various evidence-based clinical guidelines for the treatment of mental health issues have both provided guidance to primary care physicians and have also tended to constrain their roles to the making of diagnoses, providing prescriptions for medication and referral to specialty services. Often, little acknowledgment is given to evidence indicating that individual patient characteristics may be more important than protocol-driven factors in the delivery of this care [27].

Increasingly, treatment strategies focusing on long-term recovery from mental illness, with less emphasis on pathology, deficits, and medication in the treatment of these conditions are gaining ground. It is recognized that the recovery from mental illness is a highly personal and subjective experience and that clinician-centered outcomes, such as an enumeration of symptoms, might be less important in defining outcomes. The longitudinal relationship that physician and patient enjoy

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can be used to develop a meaningful narrative of the illness, out of which many possible and sometimes unexpected solutions can arise. In this paradigm of treatment, professional knowledge and resources that can include medications, social support, meaningful work, and relationships can be used as tools to facilitate the process of recovery and achieve the ultimate goal of the attainment of a life that has value and meaning to the patient.

Medications\Immunizations and Chemoprophylaxis

Many patients with mental illness will require ongoing treatment with psychotropic medications in order to maximize their social and occupational functioning. These medications, while central to treatment, can result in side effects, which may range from trivial to life-threatening. Side effects are a major cause of discontinuation of medications, and nonadherence is common [28]. Particularly among patients who are on multiple medications at high doses, the family physician must maintain vigilance for drug interactions and other adverse reactions to medications. The cost and availability of various medications may be another significant barrier to medication adherence. Community health workers or agencies may help to ensure that barriers are minimized so that interventions are not compromised.

Attention to immunization status is important, particularly among patients who are institutionalized, chronically malnourished (such as those who misuse substances) or are frankly immune compromised.

Referrals

The standard model for the treatment of difficult mental health problems in the primary care setting has been to refer the patient to a psychologist, counselor, or psychiatrist, in much the same way that any other specialty referral is made. There are several disadvantages to this approach. Chief among them is the fact that in the primary care, patients often do not follow-up with these appointments [29]. Another disadvantage is frequent suboptimal coordination and communication between providers. Discontinuities in treatments, opinions, or approaches can easily become a new source of anxiety and difficulty for the patient who may suffer from several mental and physical problems that require ongoing services for both sets of conditions. In an attempt to remediate some of these issues, the "collaborative care" model of mental health care has been piloted in a number of settings. In this model, behavioral practitioners, who may be nurse specialists, counselors, social workers, psychologists, or psychiatrists, work in a team with the physician. When a determination is made that additional and focused mental health attention is required, the physician may make a direct "warm" handoff of the patient to another mental health provider, thereby "breaking the ice" and giving the patient assurance that the carers are communicating and that the physician has confidence in the team. Close communication among members of the group, sometimes in the presence of the patient, ensures that the approach to care is as cohesive and seamless as possible. While this approach has been demonstrated to be effective for patients with depression, anxiety, and perhaps bipolar disorders in the outpatient setting, there is no evidence that it is effective in patients with schizophrenia [30, 31]. In addition, issues around the optimal implementation of these models and their cost-effectiveness are still unclear [32].

Community Mental Health Agencies

With the movement away from hospitalization and institutionalization occurring worldwide, there is an increasing need for patients to be cared for in the community. The services these agencies, organizations, or teams provide can differ but can include domiciliary and supervised care, halfway houses, day care facilities, support groups for patients and caregivers, and sheltered work. The advantages of community agencies include focused attention to the social and economic reintegration of individuals with psychiatric disorders into the community. A recent review

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suggested that there are improvements in social functioning, quality of life, and psychiatric symptoms among patients with severe mental illness who were deinstitutionalized, although these changes were modest [33].

Counseling

The delivery of counseling for mental health issues by family physicians is a time-tested strategy in primary care, providing good short-term outcomes, although long-term efficacy is less clear [34]. Advantages of the delivery of counseling by the physician in the office setting include the ability to deliver interventions in a timely and strategic manner and without necessarily having to make a potentially stigmatizing diagnosis. In recent years, a number of approaches and brief interventions have been developed that can be successfully implemented by the family physician in a time-limited encounter. These include motivational counseling, journaling, and solution-focused therapy.

Although the presence of dedicated mental health providers in the clinical setting may be very helpful in the provision of counseling to patients with mental health issues, mental health counseling that is explicitly labeled as such may be associated with stigma among patients [35]; one study showed a discrepancy among the numbers of patients who reported their willingness to receive counseling from a dedicated mental health provider versus those who actually sought and received counseling at a 1-year follow-up [36]. Another reported a significant discrepancy between provider and patient as to whether mental health counseling had been delivered [37]. Counseling for mental health issues was also significantly less likely to be delivered to African American patients in the primary care setting, although other types of counseling were delivered at equal rates in different ethnic groups [38]. Although these findings taken together may be indicative of various barriers to the delivery of mental health counseling in primary care, it could also be a manifestation of the effects of implicit negotiations between patient and physician regarding patient acceptance of various interventions.

Patient Education and Activation

Psychoeducation is a critical part of management of psychiatric disorders and, in many cases, is the only intervention required for many of the mental health conditions encountered in primary care. Education, normalization, and reassurance by the physician allow for patient and family self-regulation.

Prevention

Mental illness, like many physical illnesses, has multiple contributing causes which are poorly understood. It is clear that both heredity and environmental factors, most notably adverse childhood experiences influence the development of both physical and mental illness in adulthood [39, 40]. Various interventions to reduce exposure to adverse experiences in childhood, such as parent training programs, have been demonstrated to result in improved mental health outcomes in children. The impact of social determinants of health on the development of mental illness is increasingly recognized [41]. These factors include poverty, suboptimal housing, and poor education.

Family and Community Issues

The importance of the role of family and community in the perceptions and treatment of patients with mental health problems cannot be understated. Culture fundamentally influences the ways in which mental health problems are perceived, as well as framing the relative risks and benefits of diagnosis and treatment.

The involvement of family and other sources of informal support are often very important to recovery and should be specifically explored by the physician with the patient. These sources of

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support should be engaged as early as possible in the treatment process.

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Anxiety Disorders

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Anxiety disorders are characterized by an excessive fear response; these disorders are extremely prevalent among the general population and have a 2:1 female predilection [1]. Functional impairment is common with these disorders and, along with depression, are among the leading causes of disability and work related absences. As such, it is postulated that the economic burden of anxiety disorders is greater than any other psychiatric disorder, due to the high prevalence and cost of medical and psychiatric treatment [2]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), defines fear as "the emotional response to real or perceived imminent threat" and anxiety as "anticipation of future threat." Fear typically induces surges of autonomic arousal and thoughts of immediate danger and escape, whereas anxiety typically manifests as muscular tension and avoidant behaviors. If the anxiety creates maladaptive behaviors, physical manifestations, or mental symptoms then it becomes problematic. The anxiety disorders listed in the DSM-5 tend to be highly comorbid with other psychiatric conditions [1]. Anxiety disorders discussed in this chapter are the following: separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, and general anxiety disorder. Other anxiety disorders that do not fall under the previously mentioned disorders will briefly be discussed. In addition, obsessive-compulsive, trauma- and stress-induced related disorders will be discussed due to their relevance to anxiety. Anxiety disorders covered in this chapter are presented in Table 1 with associated ages of onset.

The DSM-5 requires a minimum of 6-month duration of symptoms that are not attributable to another medical condition and mental disorder or induced by a substance or medication to meet diagnostic criteria for anxiety disorders. An exception is noted in symptom duration for children with separation anxiety disorder and selective mutism, with a required duration of 4 weeks and 1 month, respectively. Many anxiety disorders develop in early childhood and typically persist into adulthood if not adequately treated. These disorders differ from developmentally normative fear or anxiety in magnitude of reaction or persistence beyond developmentally appropriate periods. A thorough grasp of a proper differential diagnosis and treatment of anxiety disorders can be daunting; however, it may be easier to conceptualize various anxiety disorders from the perspective of the developmental spectrum, using age of onset to help guide a differential [1, 3, 4].

Separation Anxiety Disorder

Separation anxiety disorder is the most common anxiety disorder in children under 12 years of age [1]. Approximately 90% of cases have onset before the age of 13 and the prevalence (3–4% in children) decreases as patients age [5]. Genetics and parental anxiety disorders are risk factors for developing separation anxiety disorder [6]. Primary symptoms include severe distress or anxiety from actual or possible separation from the home or attachment figure. The inappropriate fear is characterized by anxiety of potential harm toward the attachment figure or worry about events that could cause separation from the attachment figure. Separation can trigger symptoms such as crying, yelling, vomiting, and trembling. Symptoms must last for at least 4 weeks in children or 6 months in adolescence. Persistent reluctance to separate from home may lead to poor academic performance or inability to perform tasks of daily living. Repeated nightmares about separation and physical complaints of headache, nausea, or abdominal pain are common when impending separation is anticipated. The Adult Separation Anxiety Questionnaire consists of 27 questions and can be used to aid in the diagnosis of adult separation anxiety [7].

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Table 1 Summary of DSM-V Anxiety Differential by Age of Onset [1]

Disorder	Age at onset
Separation anxiety disorder	Preschool–adolescence
Selective mutism	Less than 5 years
Reactive attachment disorder	9 months–5 years
Disinhibited social engagement disorder	2 years–adolescence
Specific phobia	Early childhood age <10 years
Social anxiety disorder (social phobia)	Adolescence
Panic disorder	Early adulthood
Agoraphobia	Early adulthood
Generalized anxiety disorder	Early adulthood
Substance−/medication-induced anxiety disorder	Variable
Anxiety disorder due to another medical cause	Variable
Other specified anxiety disorders	Variable
Unspecified anxiety disorder	Variable
Obsessive-compulsive and related disorders	Late adolescence–early adulthood
Post-traumatic stress disorder	Early childhood–adulthood
Acute stress disorder	Early childhood–adulthood
Adjustment disorders	Early childhood–adulthood

Treatment can include antidepressants in severe cases, but typically symptoms of separation anxiety disorder tend to resolve over time. Parents of children with separation anxiety disorder may make significant lifestyle accommodations to relieve symptoms, that is, changing work routines, sleeping patterns [1, 8]. Negative consequences include sadness, social withdrawal, or constant demand for attention. Independent activities also may be affected (i.e., school avoidance, fear of sleeping alone, leaving for college) and should be explored. Other social stressors to consider include school bullying, bereavement, or exposure to a recent traumatic event. This disorder is often comorbid with generalized anxiety disorder, specific phobia, posttraumatic stress disorder (PTSD), social anxiety disorder, agoraphobia, OCD, and personality disorders.

Selective Mutism

Selective mutism usually presents before the age of 5 years and is characterized by a consistent failure to initiate speech in specific social situations where there is an expectation for speaking (e.g., school) even though the individual speaks in other situations [1]. Point prevalence is between 0.03 and 1% [1]. Occasionally, a diagnosis of selective mutism may be delayed until a child enters school and more attention is placed on social interactions. Diagnosis relies on input from parents and the child's teachers. The disturbance must be present for at least 1 month, but not the first month of school, and is not due to lack of knowledge of, or comfort with, the spoken language required. Communication disorders or intellectual disabilities should be considered in the differential diagnosis. Social anxiety disorder is a common comorbidity and should be identified and treated if present [1, 9].

Specific Phobias

Specific phobias involve the manifestation of marked fear, anxiety, or avoidance in the context of specific objects or situations [1]. Persons with specific phobias typically have more than one phobia. Common phobias include fear of heights, situations, or animals among others. Symptoms of specific phobias generally develop before the age of 10 after a traumatic event, but not all phobias have a specific trigger. Symptoms that persist into adulthood tend to be persistent and are unlikely to remit. Specific phobia, though low in prevalence,

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remains a commonly experienced disorder in late life. Persons with specific phobias should be referred to mental health professionals for treatment. The most common treatment is desensitization procedures starting with relaxation followed by graded exposure to the phobia.

Social Anxiety Disorder (Social Phobia)

Social anxiety disorder (social phobia) is characterized by marked fear, anxiety, or avoidance of social situations where possible scrutiny and assessment by others may occur. The average age of onset for social anxiety in the United States is 13 years. Common fears are humiliation, embarrassment, and failure. Typically, patients have anxiety anticipating public speaking and interviews. Avoidance of social situations may hinder new job, education, or promotion opportunities. Patients with social anxiety have an increased school dropout rate. Lack of employment is a strong predictor for social anxiety disorder. Depression is a common comorbidity in social anxiety disorder and may be related to the use of substances to help mitigate social fears [1].

First line treatment involves validation and reassurance from the provider. If necessary, low dose propranolol can be used as needed 30–60 min prior to social functions to relieve anticipatory anxiety [4]. Antidepressants can also be used if the anxiety is not limited to specific scenarios. If a patient requires further treatment, referral to a mental health care professional may be helpful.

Panic Disorder

Panic disorder is characterized by recurrent unexpected panic attacks that have an onset within minutes [1, 10]. It has a lifetime prevalence of 4.7%, average onset of 20–24 years, and occurs more frequently in females [5]. Typically, there is no "trigger" to the panic attack. Attacks are described as occurring suddenly. Patients are unable to control the panic attack with willpower alone. Diagnosis requires an abrupt onset, within minutes, of 4 or more symptoms. Manifested symptoms include tachycardia, diaphoresis, tremor, shortness of breath, sensation of choking, chest pain or discomfort, nausea, abdominal distress, dizziness, lightheadedness, chills or a sensation of heat, paresthesia, derealization or depersonalization, fear of losing control or dying. Culture-specific symptoms may occur (e.g., tinnitus, screaming, crying) but they do not count as DSM diagnostic criteria. The panic attack must then be followed by 1 or more months of at least one of the following: continued anxiety about additional panic attacks or maladaptive change in behavior related to the attack. The diagnosis must not be related to substance abuse or another medical condition. Panic disorder may lead to fear of leaving home (agoraphobia) in some cases. Panic disorder is frequently comorbid with other anxiety disorders, depression, and bipolar disorder. Panic disorder is associated with high levels of social, occupational, and physical disability. Individuals with panic attacks or a diagnosis of panic disorder in the past 12 months have a higher risk of suicide [1].

Agoraphobia

Agoraphobia is defined as fear or anxiety about being in open spaces (e.g., public venues), standing in line or in a crowd, using public transportation, or being alone outside the home [1]. Agoraphobia is associated with panic disorder. It is differentiated from other anxiety disorders since sufferers specifically fear that help may not be readily available in the event of a panic attack. The onset of agoraphobia is typically early adulthood, as is the case with panic disorder. The situational fear encompasses thoughts of being unable to escape or of being embarrassed due to manifestations of their anxiety. The course is typically persistent and chronic, with only 10% of cases remitting spontaneously. Approximately one third of affected adults are homebound and unable to work. Common comorbidities include other anxiety disorders, depressive disorders, PTSD, and alcohol use disorder.

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Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive and persistent worry that is difficult to control, causes significant distress or impairment, and occurs most days for at least 6 months [1]. The worry is attributable to multiple events or activities and has three of the following symptoms: restlessness, easily fatigued, difficulty concentrating, irritability, increased muscle tension, sleep disturbance. It is one of the most common mental disorders in the primary care setting [11]. GAD is twice as common in women as it is in men and is the most common anxiety disorder among the elderly population [12, 13]. The typical age of onset is early adulthood. Lifetime prevalence in the United States is estimated to be between 5.1 and 11.9% [5, 14]. GAD often presents with comorbid substance abuse, PTSD, and obsessive-compulsive disorder (OCD). Additionally, major depressive disorder that is comorbid with GAD portends a more severe and prolonged course of illness and a greater functional impairment [14]. GAD is also common among patients with chronic pain and with unexplained chronic physical illness [1, 3]. Differentials include OCD, panic disorder, somatoform disorders, paranoid psychotic disorders, eating disorders, and various personality disorders. Negative outcomes that may be exacerbated by untreated GAD include increased blood pressure and coronary artery disease.

Other Anxiety Disorders

This group of disorders includes the following: substance- or medication-induced anxiety disorder, anxiety disorder due to another medical cause, other specified anxiety disorders, and unspecified anxiety disorder [1]. Substance- or medication-induced anxiety disorder presents with symptoms of panic and anxiety that developed during or immediately following intoxication or withdrawal of a substance or medication. Anxiety disorder due to another medical condition is explained by the physiological effect of the underlying medical condition (e.g., hyperthyroidism, arrhythmia, asthma, seizure disorders).

Other specified anxiety disorders and unspecified anxiety disorders do not fit into the criteria for one of the aforementioned anxiety disorders.

Obsessive-Compulsive and Related Disorders

This group of disorders includes obsessive-compulsive disorder (OCD), body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, substance- or medication-induced OCD, OCD due to another medical condition, and unspecified OCD. The age of onset is typically late adolescence or early adulthood, but can present in late childhood as well. The presence of recurring intrusive and persistent thoughts (obsessions) and repetitive behaviors or mental acts (compulsions) are a hallmark of this collection of disorders. The specifics of OCD vary by individual, but there are common themes which include contamination obsessions and cleaning compulsions; symmetry obsessions with repeating, ordering, and counting compulsions; religious, aggressive, or sexual obsessions and related compulsions; and harm obsessions and related compulsions [1, 15].

Body dysmorphic disorder is characterized by a perceived flaw in physical appearance that is minor or absent. Repetitive acts of checking the mirror, excessive grooming, and reassurance-seeking behaviors are common [1].

Hoarding disorder is described as significant difficulty with discarding possessions, irrespective of value, resulting in an intense need to save items. Symptoms include accumulation of items that congest and clutter living spaces to the point that their intended use is compromised [1, 7].

Trichotillomania (hair-pulling) disorder involves recurrent hair pulling with resultant hair loss, despite repeated attempts to stop the behavior. Excoriation (skin-picking) disorder involves recurrent picking of the skin despite repeated

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attempts to cease. These two disorders are usually preceded by feelings of anxiety or boredom [1, 7, 16].

Substance- or medication-induced OCD involves symptoms related to intoxication or withdrawal of a substance or medication. Symptoms resulting from OCD due to another medical condition are specifically associated with that medical condition. Other specified OCDs and unspecified OCD have atypical presentations and uncertain etiologies which do not meet criteria for diagnoses listed above [17].

Trauma- and Stressor-Related Disorders

Reactive Attachment Disorder

Reactive attachment disorder typically presents between the ages of 9 months and 5 years and is characterized by noticeably inappropriate or disturbed attachment behaviors [1]. Children must be at a developmental age of at least 9 months for diagnosis as the child must be able to make selective attachments. The exact disorder prevalence is unknown due to difficulty in case identification but it is uncommon. Children with reactive attachment disorder rarely or minimally turn preferentially to an attachment figure for comfort, support, or nurturance. Behaviors absent in the individual are an absence of expected comfort seeking and lack of response to comforting behaviors. When distressed, children with the disorder show no consistent effort to obtain comfort, support, nurturance, or protection from caregivers. Children with reactive attachment disorder have diminished or absent positive emotions when comforted by caregivers. Unexplainable negative emotions can occur such as episodes of fear sadness, or irritability. This disorder is commonly comorbid with social neglect (e.g., malnutrition) and developmental delay [1]. Differentials include autism spectrum disorder, intellectual disability, and depressive disorders. Adolescent patients presenting with similar symptoms to reactive attachment disorder likely have a separate psychiatric disorder as it is unknown whether it occurs in older children [18].

Disinhibited Social Engagement Disorder

Disinhibited social engagement disorder is characterized by culturally inappropriate and overly familiar behavior with relative strangers [1]. The inappropriate behavior may be verbal or physical and include willingness to venture away to unfamiliar settings or follow an unfamiliar adult without hesitation. Children with the disorder often have patterns of neglect that are presumed to be responsible for the abnormal behavior. As with reactive attachment disorder, children must be at least 9 months of age for diagnosis. The disorder usually presents at 2 years of age to adolescence. It is persistent if it lasts for longer than 12 months. The disorder is rare, occurring in only 20% of children with a history of severe neglect and raised in foster care or in institutions. Differential includes attention-deficit/hyperactivity disorder, but patients with disinhibited social engagement disorder do not demonstrate hyperactivity or inattention. Children may have comorbid cognitive delays, language delays, or stereotypies.

Post-Traumatic Stress Disorder (PTSD)

The hallmark of PTSD is the development of specific symptoms when exposed to one or more traumatic events involving actual or threatened death, serious injury, or sexual violation [1]. Older data suggest approximately 60.7% of men and 51.2% of women in the USA report at least one traumatic event in their lifetime [19]. Lifetime morbidity risk for PTSD is estimated to be 10.1% of the population [20]. The prevalence of PTSD is highest in those with increased risk of traumatic exposure, such as veterans, police, firefighters, emergency medical personnel, and victims of violent crime or rape. Symptoms of PTSD vary in clinical presentations and may involve dysfunction in five domains: intrusive thoughts, mood changes, dissociative

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reactions, avoidance, and marked alterations in arousal. Symptoms can begin within 3 months after exposure to a traumatic event; however, symptoms can also present much later before full criteria for a diagnosis of PTSD are met. Several diagnostic scales are available. Similar conditions that do not meet all the requirements for PTSD are acute stress disorder and adjustment disorder [1]. Examples of comorbid conditions with PTSD include depression, substance use disorders, and somatic symptoms. Psychotherapy is the preferred treatment option, and consideration should be given to refer these patients to a mental health provider for treatment. Second-line therapy includes antidepressants which are discussed in more detail below.

Screening Tools for Anxiety Disorders

The Hamilton Anxiety Rating Scale (HAM-A) (Fig. 1) and the Generalized Anxiety Disorder 7-item Scale (GAD-7) (Fig. 2) are two tests that are used to screen for possible anxiety in the clinical setting (Figs. 1 and 2, respectively). The HAM-A includes 14 items which measure psychic and somatic symptoms of anxiety. Each item is scored from 0 (not present) to 4 (severe), with a total score range of 0–56. Less than 17 indicates mild severity, 18–24 mild to moderate severity, and 25–30 moderate to severe. The HAM-A is most useful for gauging the response of anxiety to treatment [19]. It has been criticized, however, for its lack of discrimination between anxiety and depressive symptoms [20]. The GAD-7 has been identified as a useful tool with validity for identification of probable cases of generalized anxiety disorder [21, 22].

Both the GAD-7 or HAM-A can be used to monitor symptoms objectively at follow-up in practice; however, neither of these scales have been validated for monitoring purposes in trial data [23]. If the scales are being used for follow-up, a patient must complete the same scale they used in diagnoses. An adequate threshold for successful treatment is at least a 50% reduction from baseline symptoms, with the overall goal being remission, which is rare.

Panic disorder can be screened with either the Panic Disorder Screener (PADIS), a point-based scale, or the PHQ-Panic Screener, yes or no answers [24, 25]. Screening for panic disorder is similar to GAD. The PADIS has a 77% sensitivity and 84% specificity, whereas the PHQ-Panic Screener has a 57% sensitivity and 91% specificity. Both scales can also be used to measure patient treatment progress at follow-up, but the same scale should be used for comparison.

Treatment

The recommended first-line treatment for anxiety and related disorders is listed in Table 2. In general, the greatest therapeutic benefit is derived from combined pharmacotherapy and psychological therapy [15, 26]. Achieving true remission is rare in these disorders. Goal-directed therapy should be emphasized [26]. Anxiety is thought to be mediated by serotonin abnormalities; therefore, medications with some serotonin activity are used for treatment [32]. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) treat a broad spectrum of symptoms and have efficacy for common comorbidities, making them excellent first-line options [15, 26]. Screening for suicidal ideation, homicidal ideation, and previous manic episodes must be negative and documented before initiation of SSRIs or SNRIs as these medications can worsen those symptoms. Patients should also be counseled on potential drowsiness. Pharmacotherapy is started at the lowest dose possible and titrated up slowly to minimize adverse effects and determine the lowest effective dose [27].

The most common adverse effects with SSRIs are sexual dysfunction, drowsiness, sleepiness, weight gain (1 to 6 pounds), dry mouth, insomnia, fatigue, nausea, dizziness, lightheadedness, and tremor [33, 34]. Sexual dysfunction includes decreased desire, arousal, and orgasm and occurs in approximately 60% of patients but resolves spontaneously in one fifth of patients at 6 months [35]. Most patients (~70%) have sexual dysfunction symptoms alleviated after a 50% dose decrease, otherwise switching to a non-SSRI can

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Hamilton Anxiety Rating Scale (HAM-A) [19]

Below is a list of phrases that describe certain feeling that people have. Rate the patients by finding the answer which best describes the extent to which he/she has these conditions. Select one of the five responses for each of the fourteen questions.

0 = Not present, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very severe.

1	**Anxious mood**	0	1	2	3	4	8	**Somatic (sensory)**	0	1	2	3	4
	Worries, anticipation of the worst, fearful anticipation, irritability.							Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation.					
2	**Tension**	0	1	2	3	4	9	**Cardiovascular symptoms**	0	1	2	3	4
	Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax.							Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat.					
3	**Fears**	0	1	2	3	4	10	**Respiratory symptoms**	0	1	2	3	4
	Of dark, of strangers, of being left alone, of animals, of traffic, of crowds.							Pressure or constriction in chest, choking feelings, sighing, dyspnea.					
4	**Insomnia**	0	1	2	3	4	11	**Gastrointestinal symptoms**	0	1	2	3	4
	Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors.							Difficulty in swallowing, wind abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation.					
5	**Intellectual**	0	1	2	3	4	12	**Genitourinary symptoms**	0	1	2	3	4
	Difficulty in concentration, poor memory.							Frequency of micturition, urgency of micturition, amenorrhea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence.					
6	**Depressed mood**	0	1	2	3	4	13	**Autonomic symptoms**	0	1	2	3	4
	Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing.							Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair.					
7	**Somatic (muscular)**	0	1	2	3	4	14	**Behavior at interview**	0	1	2	3	4
	Pains and aches, twitching, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone.							Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, etc.					

Fig. 1 Hamilton Anxiety Rating Scale (HAM-A)

help. Nausea occurs in 60% of patients, sertraline is the greatest offender [36]. Of the SSRIs, fluoxetine causes the most insomnia and agitation and generally should be avoided in treating anxiety conditions. Rare adverse effects of SSRIs include bleeding (1 bleed per 8000 prescriptions), serotonin syndrome, extrapyramidal symptoms (fluoxetine is the worst offender), and syndrome of inappropriate antidiuretic hormone secretion [37]. No recommendations are available to prevent serotonin syndrome, but it is good practice to limit the number of serotonin acting agents. The physician should be cognizant of possible early serotonin syndrome with new onset tremors, mydriasis, hyperactive bowel sounds, diaphoresis, skin color changes, and

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Generalized Anxiety Disorder 7-item (GAD-7) scale [21, 22]

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	
Somewhat difficult	
Very difficult	
Extremely difficult	

Fig. 2 Generalized Anxiety Disorder 7-item (GAD-7) scale

lower extremity hyperreflexia when a patient is taking an SSRI or SNRI [38].

Most of the adverse effects with SSRIs are the same with SNRIs; however, sexual dysfunction is less frequently reported. Supine diastolic blood pressure (DBP) should be regularly monitored for patients taking SNRIs. Venlafaxine at higher doses can increase supine DBP by 10 to 15 mg DBP in 13% of patients. Generally systolic blood pressure is minimally affected. Duloxetine is associated with less hypertension (~2 mmHg DBP increase) than venlafaxine, does not cause weight gain, and also has an indication for neuropathic pain which may of benefit in selected patients.

No universal approach for switching or discontinuing antidepressants exists. However, good practice suggests SSRIs and SNRIs can be directly interchanged at equivalent doses [39]. Discontinuation of SSRIs and SNRIs should be performed over at least 4 weeks as abrupt cessation can cause flu-like and neurologic symptoms. Paroxetine and venlafaxine require longer tapers (25% reduction every 4 to 6 weeks) due to their comparatively shorter half-lives.

Other antianxiety medications include the tricyclic antidepressant doxepin and buspirone. Both have limited efficacy and should be limited as second line options after SSRIs and SNRIs have been trialed at appropriate doses and duration (4 to 6 weeks at the maximum dose). Benzodiazepines are inappropriate maintenance therapy for anxiety disorders [40]. Keeping

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Table 2 First-line treatment of anxiety and related disorders [4, 15–17, 26–31]

Diagnosis	Treatment(s)	Comments
Anxiety disorders		
Separation anxiety disorder	SSRI 1. Fluoxetine (Prozac) up to 40 mg/day[a]. 2. Paroxetine (Paxil) up to 50 mg/day[b]. Psychotherapy 1. CBT[c]	Currently, no FDA-approved medications for separation anxiety; however a trial of SSRI is considered reasonable
Selective mutism	SSRI 1. Fluoxetine (Prozac) up to 60 mg/day Psychotherapy 1. CBT[c]	
Specific phobias	Psychotherapy 1. Exposure therapy[d]	
Social anxiety disorder	SSRI 1. Paroxetine (Paxil). 2. Sertraline (Zoloft). SNRI 1. Venlafaxine (Effexor) Psychotherapy 1. Exposure therapy[d]	
Panic disorder	Psychotherapy 1. CBT[c] SSRI 1. Fluoxetine (Prozac). 2. Paroxetine (Paxil). 3. Sertraline (Zoloft). SNRI 1. Venlafaxine (Effexor)	
Agoraphobia	Psychotherapy 1. Exposure therapy[d]	
Generalized anxiety disorder	SSRI 1. Escitalopram (Lexapro). 2. Paroxetine (Paxil). SNRI 1. Duloxetine (Cymbalta). 2. Venlafaxine (Effexor).	
Obsessive-compulsive and related disorders		
Obsessive compulsive disorder	SSRI 1. Fluoxetine (Prozac). 2. Sertraline (Zoloft). 3. Paroxetine (Paxil). Psychotherapy 1. CBT[c]	Higher doses of SSRI treatment are often needed in some cases
Body dysmorphic disorder	Psychotherapy 1. CBT[c]	
Hoarding disorder	SSRI 1. Paroxetine (Paxil) TCA 1. Clomipramine	No specific pharmacotherapy can be recommended strongly at present; however, a trial of an SSRI is considered reasonable
Trichotillomania	SSRI 1. Fluoxetine (Prozac) Antipsychotics 1. Aripiprazole (Abilify). 2. Quetiapine (Seroquel).	

(continued)

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Table 2 (continued)

Diagnosis	Treatment(s)	Comments
	Supplements 1. N-acetylcysteine (dosing range, 1200–2400 mg/day) Psychotherapy 1. HRT[e]	
Excoriation disorder	SSRI 1. Fluoxetine (Prozac)	
Trauma-and stressor-related disorders		
Post-traumatic Stress disorder	SSRI 1. Paroxetine (Paxil) 2. Sertraline (Zoloft) Psychotherapy 1. Exposure therapy	

[a]Ages 7–17 years
[b]Ages 8–18 years
[c]CBTcognitive behavioral therapy. Emphasizes the relationship between cognitions (thoughts), somatic experiences (physical complaints), and behavior in anxiety-provoking situations
[d]Exposure therapy. Utilizes repeated exposure to feared stimuli and memories surrounding a traumatic event and aims to help the patient to experience a decrease in fear and an increase in mastery of anxiety symptoms by incorporating mental processing, psychoeducation, and breathing relaxation exercises
[e]HRT habit reversal therapy. A CBT approach that consists of awareness training and stimulus control

benzodiazepines on an as-needed basis for routine anxiety-provoking situations can reinforce the fear response and should be avoided. However, single dose benzodiazepines may be appropriate for some patients in specific scenarios (e.g., air travel, surgery). If a benzodiazepine must be used for severe cases, clonazepam is preferred as it has a slower onset of action and longer half-life, thus reducing the phenomenon of rebound anxiety, which is sometimes seen with other agents.

Over-the-counter herbal remedies may be considered as adjunctive therapy. The most common agents include valerian (Valeriana officinalis), kava (Piper methysticum), passionflower, St. John's wort (Hypericum perforatum), and Rhodiola rosea. While efficacy and robust safety data are lacking, the risk benefit ratio should be discussed with patients.. Due to the concern of potential liver toxicity with the use of kava, a double-blind, randomized, placebo-controlled study showed kava to be well tolerated, except for a small increase in headaches, and was moderately effective for GAD [28]. St. John's Wort is commonly used by patients but may have significant interactions with medications including antiretrovirals, immunosuppresants, antineoplastics, anticoagulants, oral contraceptives, and hormone replacement medications.

Treatment for panic disorder includes patient counseling on panic disorder, and specific assurances that the panic attacks are not dangerous despite symptoms [41]. Referral should be made to mental health care providers for cognitive behavioral therapy. Benzodiazepines may be used briefly, but should be tapered rapidly as the effect of antidepressants ramp up.

Complementary and Alternative Methods

Yoga

Yoga is an ancient Asian practice that has become increasingly popular in Western culture. It incorporates meditation and postures and connects individuals with mindful breathing. It is meant to improve the symbiotic relationship between mind, body, and soul. It has been used for centuries to calm the mind, which is an essential part of the

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practice. There are various forms of practice, but all serve to have the same basic teachings that focus on poses, breathing techniques, and meditation. Several review articles looking at randomized and nonrandomized trials have concluded that practicing yoga can reduce anxiety and overall stress levels [42, 43].

A systematic review of 17 peer-reviewed articles published from 2011 to 2013 concluded that yoga is a promising modality for stress management. Twelve of the 17 articles reviewed were randomized control trials. The number of subjects ranged from 20 to 205. The outcome measures, length of treatment, and type of yoga varied greatly among the studies [44]. This systematic review did not address any particular anxiety disorder diagnosis.

Exercise

Physical activity may provide psychological benefits of improvement in skills, body image, and physical fitness that can enhance self-esteem [45]. Aerobic exercise provides psychological benefits of self-mastery, goal attainment, and socialization.

Data suggests aerobic exercise is effective in the treatment of those with diagnosed anxiety disorder or clinically elevated anxiety levels on a validated rating scale [46]. High-intensity exercise seems to have greater anxiety relief effects than low-intensity. Additional studies suggest that exercise is more effective than control in reducing anxiety symptoms [47].

Acupuncture

Traditional Eastern Medicine encompasses several modalities, including acupuncture. The practice has become more common in Western society, usually in conjunction with allopathic and osteopathic practices. Acupuncture uses specific points in the body that are all connected to one's individual "Qi" or life energy. The insertion of needles into these points alters the "flow" which can serve to aid a particular ailment related to that point. Although acupuncture has been studied in the use of chronic pain, when it comes to treatment of anxiety disorders, there is still very little evidence for efficacy. Concerns that frequently arise are if there is a consensus on which points are directly related to anxiety, the type of acupuncture used (needling vs cupping), duration and frequency of treatments, and appropriate control groups [48].

Mindfulness

The term mindfulness originates from the ancient Indo-Aryan Pali word "sati" meaning having awareness, attention, and remembering [49]. The notion of mindfulness is thought to reach back to Buddhist concepts, but has developed into a more modern definition of moment-to-moment awareness of one's experience without judgment [49]. Mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) merge Eastern practices of mindfulness with Western cognitive-behavioral practice [50]. Review of randomized control trials comparing mindfulness treatments including MBSR and MBCT with active control conditions has shown mindfulness-based interventions to be effective in treating a number of conditions including depression, anxiety, and chronic pain [50].

Daily situations in which this can be practiced include while driving a car, washing dishes, or in a more defined setting such as meditation sessions. More recently, online mindfulness-based interventions (MBIs) have become available and are an option for those who may be unable to participate in face-to-face settings. A meta-analysis of the effects of online MBIs suggests evidence of efficacy for programs that improve mental health outcomes, with smaller effects on anxiety and depression with a more notable effect on stress [51].

Summary

Anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders account for significant morbidity and mortality. Specifically, the anxiety disorders

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account for the majority of cost burden due to their high prevalence and the increasing cost of appropriate therapies. Timely and accurate diagnoses followed by appropriate treatment are of the utmost importance due to the pervasive nature of these disorders and their effects. Most disorders are best treated with combined therapies: for example, CBT or exposure therapy coupled with pharmacotherapy. Alternative herbal therapies lack significant efficacy data but are often considered safe for use and may be considered if interactions are avoided. Regular physical exercise is an effective intervention that has multiple beneficial effects on overall health. While strong evidence may be lacking for yoga and acupuncture, data seems to indicate a positive effect on the course of anxiety disorders, and they should be considered as adjuncts to treatment for patients who are open to them. Mindfulness techniques appear to have the most robust support from current evidence, which is not surprising given the degree of overlap with the well-established practice of CBT.

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Mood Disorders

32

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Depressive and bipolar disorders are medical conditions which are often first diagnosed and treated in primary care settings [1, 2]. Hence, family physicians are in a frontline position to provide optimal care for patients who suffer from these disorders. This chapter will provide succinct and practical information on the diagnosis and most effective pharmacologic and nonpharmacologic treatments of these disorders in a primary care setting. Newer therapies, such as deep brain stimulation, as well as consideration of special populations, will also be discussed.

Epidemiology

Mood disorders, such as major depressive disorder, persistent depressive disorder (PDD; formerly dysthymic disorder), and bipolar disorders are quite common [3]. The lifetime prevalence of having any type of mood disorder is 20%. In 2012, it was estimated that 10.4 million adults aged 18 or older in the USA had at least one major depressive episode resulting in severe impairment in the past year. This represented 4.5% of all US adults (see Fig. 1).

In general, mood disorders are more common in women, in those with a family history of psychiatric illness, and in those individuals who have comorbid medical disorders. The majority of patients with mood disorders first present to nonpsychiatrists, such as family physicians, often complaining of somatic, rather than mood symptoms (e.g., pain, GI upset, headache, etc.).

Risk and Prognostic Factors

While the exact causes of depressive and bipolar disorders remain unclear, risk factors have been identified for the development of depressive disorders and classified into three major categories. These are temperamental, environmental, and genetic/physiological. Within these areas, neuroticism (negative affectivity), adverse childhood events, and a family history of depression are some of the strongest risk factors [4]. First-degree relatives of people with major depression (MD) have an increased risk of MD. The variance in liability to MD is accounted for by additive genetic effects and environmental influences specific to an individual [4].

A family history is also one of the strongest risk factors for bipolar disorders, and there is an average tenfold increased risk among first-degree adult relatives of individuals with bipolar I or bipolar II disorders [5]. Twin studies are generally consistent in observing greater concordance among monozygotic twins than dizygotic twins, which may provide evidence that susceptibility genes contribute to the familiality of bipolar disorder [6].

Bipolar I disorders are also more common in countries with a higher socioeconomic status and among separated, divorced, and widowed individuals than married or single individuals, although the direction of this association remains unclear [4].

Psychological theories propose the idea that individuals with these disorders are more likely to engage in more "depressogenic" cognitive styles and more cognitive distortions in response to stressors than do nondepressed individuals. In addition, newer theories are evolving which examine the role of inflammatory markers resulting from oxidative stress and the negative impact of poor nutrition on the development and maintenance of these disorders, as well as other genetic, physiologic, and environmental precursors of depressive and bipolar disorders.

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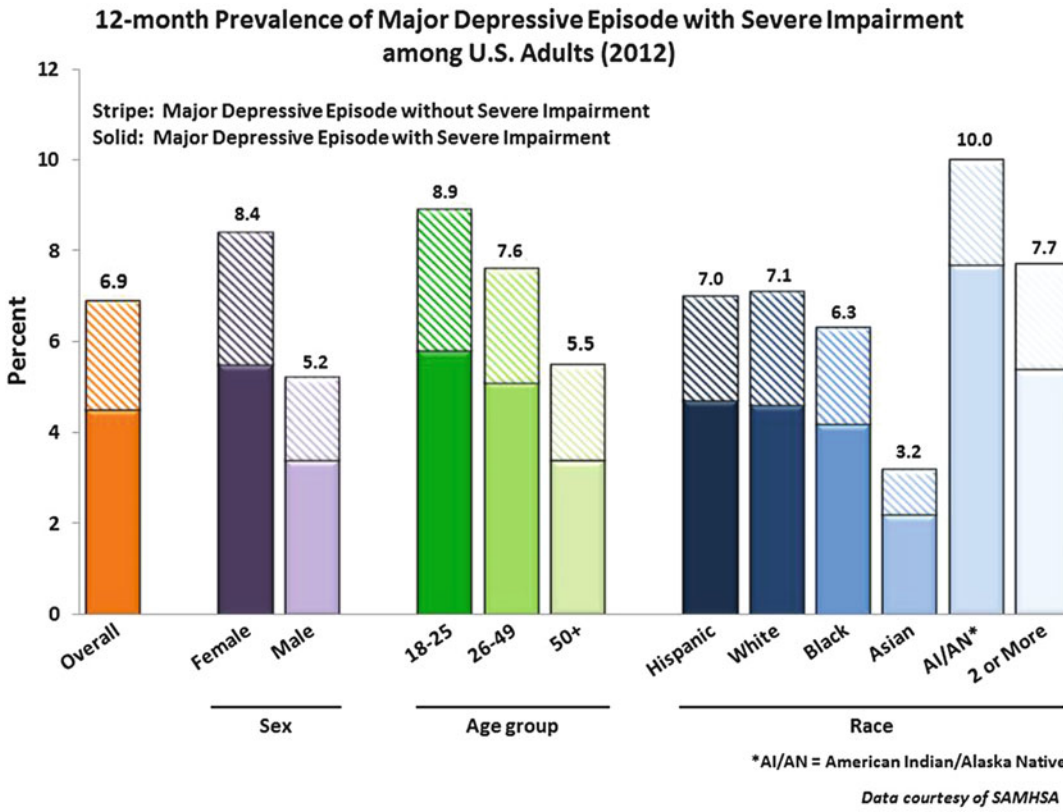


Fig. 1 National Institutes of Health 2012. Results from the 2012 National Survey on Drug Use and Health: http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-with-severe-impairment-among-adults.shtml

Diagnostic Criteria

Depressive Disorders

The *Diagnostic and Statistical Manual* of the American Psychiatric Association Fifth Edition (DSM5) divides mood disorders into two categories: depressive disorders and bipolar and related disorders [4]. A major depressive disorder is diagnosed if the patient has experienced depressed mood or loss of interest and at least four additional symptoms (see Fig. 2) for at least 2 weeks and has never experienced a manic, hypomanic, or mixed episode.

In children and adolescents, the mood may be irritable rather than sad. Once the diagnosis has been made, specifiers which note severity, course, and specific aspects of the depressive episode (including psychotic features, anxious distress, peripartum onset, and others) are also noted. As with all DSM-5 disorders, symptoms cannot be due to another psychiatric disorder, physiological effects of a substance, or another medical illness and must cause clinically significant distress or impairment in important areas of functioning.

In *persistent depressive disorder*, formerly "dysthymic disorder," the essential feature is a depressed mood that occurs for most of the day, for more days than not, for at least 2 years (at least 1 year for children and adolescents). This disorder represents a consolidation of DSM-IV-defined chronic major depressive disorder and dysthymic disorder in the DSM-5. Major depression may precede persistent depressive disorder, and major depressive episodes may occur concomitantly during persistent depressive disorder. Individuals whose symptoms meet major depressive disorder

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DSM-5 Criteria for Major Depressive Disorder and Persistent Depressive Disorder (Dysthymia)

MAJOR DEPRESSIVE DISORDER

5 or more symptoms must have been present in the same 2-week period and represent a change in previous functioning (at least 1 of the symptoms is depressed mood or loss of interest):

1. Depressed mood most of the day, nearly every day (observed or subjective)
2. Markedly diminished interest or pleasure
3. Significant weight loss or weight gain or change in appetite
4. Sleep disturbance (insomnia or hypersomnia)
5. Psychomotor retardation or agitation nearly every day (observed)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or inappropriate/excessive guilt
8. Impaired ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death, suicidal ideation, or a suicide attempt or specific plan for committing suicide.

- *Mood can be irritable in children and adolescents*
- *Has never had a manic or hypomanic episode in the past*

PERSISTENT DEPRESSIVE DISORDER (DYSTHYMIA)

Depressed mood most of the day nearly every day, for more days than not, for at least 2 years (observed or subjective). During this 2-year period, the individual has never been without the symptoms for more than 2 months at a time.

Presence, while depressed, of 2 or more of the following symptoms during the same period:

1. Poor appetite or overeating
2. Insomnia or hypersomnia
3. Low energy or fatigue
4. Low self-esteem
5. Poor concentration or indecisiveness
6. Feelings of hopelessness

- *Mood can be irritable and duration must be 1 year or longer in children and adolescents)*
- *Has never had a manic or hypomanic episode in the past*

A useful mnemonic to aid in diagnosis is SIG:ECAPSS ("prescribe energy capsules"). These stand for Sleep changes (insomnia or hypersomnia), Interest (loss of), Guilt (or worthlessness), Energy (fatigue), Concentration (impaired), Appetite (decreased or increased), Psychomotor (retardation or agitation), Suicidal ideation (and plan or intent) and Sex (decreased libido).

Fig. 2 DSM-5 criteria for major depressive disorder and persistent depressive disorder (dysthymia)

criteria for 2 years should also be given a diagnosis of persistent depressive disorder in addition to major depressive disorder, a diagnosis often termed, "double depression."

In primary care, a large number of patients present with somatic, rather than mood, symptoms. It is important that the family physician ask patients who present with insomnia and

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fatigue about accompanying depressive symptoms. In addition, depression is often comorbid with, or can result from, other medical conditions or due to the side effects of medications. In the DSM-5, subthreshold depressive symptoms which meet many but not all the criteria for a depressive disorder can also occur and is now termed "unspecified" rather than "not otherwise specified." Once depression is suspected, it is of critical importance to also assess whether or not the patient has experienced a manic, hypomanic, or mixed episode in the past, as treatment for unipolar and bipolar depression differs significantly.

In addition to taking a detailed history and using SIGECAPS as a mnemonic, there are short assessment instruments readily available online at no cost. One of these, the Brief Patient Health Questionnaire (PHQ-9) [7], is widely available and has a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively [7]. This brief assessment has been translated into many different languages and is available here: http://phqscreeners.com/pdfs/02_PHQ-9/English.pdf.

Scoring instructions for the PHQ-9 are available at http://www.phqscreeners.com/instructions/instructions.pdf.

It should be noted that the PHQ-9 is only a screening test for depression. If positive, the clinician should then conduct a careful diagnostic interview, using DSM-5 criteria, to make a diagnosis of a depressive disorder.

The most recent (2016) US Preventive Services Task Force (USPSFTF) guidelines recommend screening adults (18 and older), including pregnant and postpartum women, for depression when adequate systems are in place to ensure accurate diagnosis, effective treatment and follow-up (please see https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/depression-in-adults-screening). "'Staff-assisted depression care supports' refer to clinical staff that assist the primary care clinician by providing some direct depression care, such as care support or coordination, case management, or mental health treatment." Per the USPSTF report, "the lowest effective level of staff-assisted depression care supports consisted of a screening nurse who advised resident physicians of positive screening results and provided a protocol that facilitated referral to behavioral treatment." (Please see http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/depression-in-adults-screening.)

Bipolar and Related Disorders

Bipolar disorders are often underdiagnosed in primary care. In the DSM-5, three distinct types of bipolar disorders are recognized: bipolar I disorder, bipolar II disorder, and cyclothymic disorder. As with the depressive disorders, categories for the diagnosis of substance-induced mood disorders, bipolar, and related disorder due to another medical condition and unspecified bipolar and related disorders are also available in the DSM-5.

Bipolar I Disorder

Bipolar I disorder is the most severe form of this illness. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder, even though this manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. While the overwhelming majority of those with bipolar I disorder also have episodes of major depression, only the presence of a manic episode is needed to make this diagnosis.

DSM-5 criteria for a manic episode include:

A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (any duration if hospitalization is necessary). During this period, three (or more) of the following symptoms (four if the mood is irritable) are present:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep
3. More talkative than usual or pressure to keep on talking

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4. Flight of ideas or racing thoughts
5. Distractibility
6. Increase in goal-directed activity (or psychomotor agitation)
7. Excessive involvement in activities that have a high potential for painful consequences (spending money, sexual indiscretions, substance abuse, etc.)

These symptoms must represent an unequivocal change in functioning and cannot be due to another psychiatric illness, physiological effects of a substance, or another medical condition and must cause significant distress and impairment in functioning.

Note: A useful mnemonic to aid in the diagnosis of a manic episode is DIGFAST (see Fig. 3).

Once the diagnosis of bipolar I disorder has been made, specifiers for the current or most recent episode (manic, hypomanic, depressed, or unspecified), as well as severity (mild, moderate, severe, psychotic, remission), are also recorded. Additional specifiers are then noted if applicable (rapid cycling, anxious distress, mixed features, psychotic features, and others).

Bipolar II Disorder

Bipolar II disorder consists of a pattern of recurring mood episodes consisting of one or more major depressive episodes and at least one hypomanic episode:DSM-5 Hypomanic Episode. For a diagnosis of bipolar II disorder, a patient must meet the criteria for a current or past hypomanic episode and a current or past major depressive episode.

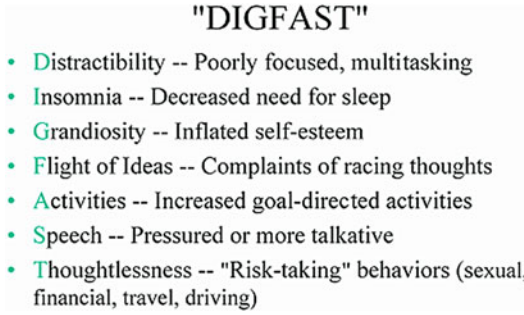


Fig. 3 DIGFAST

A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day. During this period, three (or more) of the following symptoms (four if the mood is irritable) are present:

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep
3. More talkative than usual or pressure to keep on talking
4. Flight of ideas or racing thoughts
5. Distractibility
6. Increase in goal-directed activity (or psychomotor agitation)
7. Excessive involvement in activities that have a high potential for painful consequences (spending money, sexual indiscretions, substance abuse, etc.)

These symptoms must represent an unequivocal change in functioning and cannot be due to another psychiatric illness, physiological effects of a substance, or another medical condition and must cause significant distress and impairment in functioning. Please see previous section for criteria for major depressive episode.

In order to make this diagnosis, the major depressive episodes must last at least 2 weeks, with symptoms present more days than not, and the hypomanic episodes must last at least 4 days. As with bipolar I disorder, the patient may not perceive their elevated mood as problematic; however, others (family members, co-workers) may be quite distressed by the individual's unstable behavior. Patients with bipolar II disorder often first present with major depression, which again underscores the importance of asking about a previous history of manic or hypomanic episodes. A mnemonic which can be used to help to differentiate unipolar from bipolar depression is WHIPLASHED (see Fig. 4).

Cyclothymic Disorder

A diagnosis of cyclothymic disorder is given when a patient has numerous episodes of hypomanic and depressive symptoms over the course

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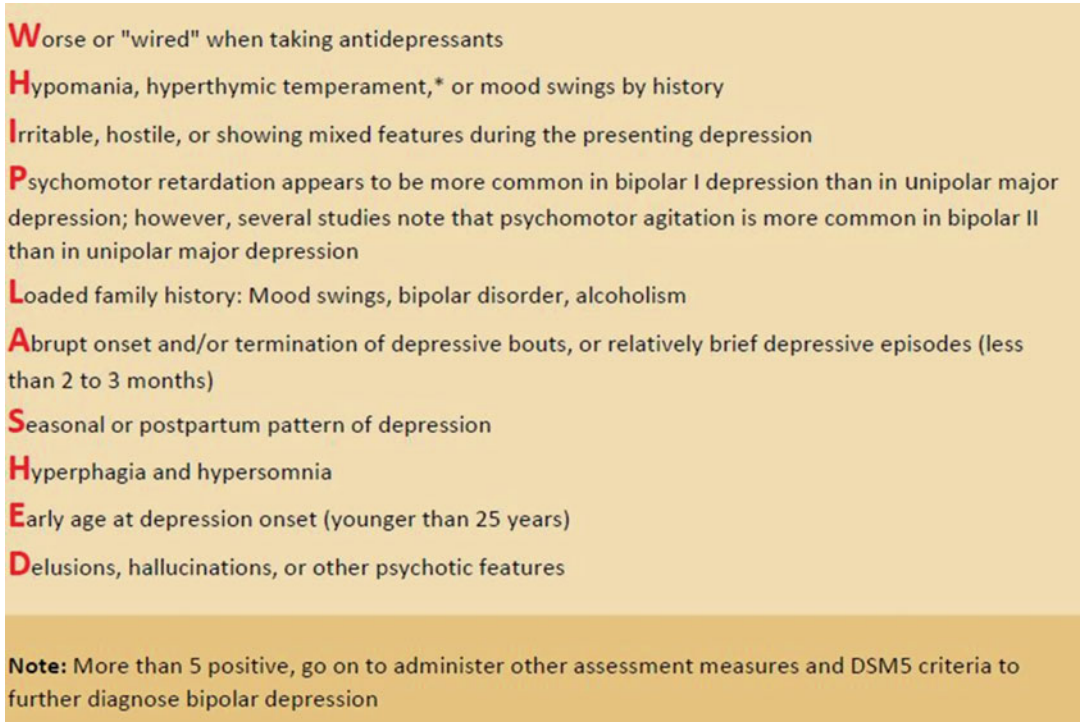


Fig. 4 WHIPLASHED screen for bipolar depression [8]

of at least 2 years (or 1 year in children and adolescents) which do not meet the full criteria for a diagnosis of a bipolar or depressive disorder but cause a significant impairment in functioning. Cyclothymic disorder is a bipolar spectrum disorder which usually begins in adolescence or early adulthood. There is a 15–50% risk that an individual with this disorder will subsequently develop bipolar I or bipolar II disorder [4]. This diagnosis might be considered for those patients whose clinical symptoms cause concern yet who do not demonstrate a positive screen on assessment measures.

The authors highly recommend using the *The Pocket Guide to the DSM-5 Diagnostic Exam* to aid in diagnosing depressive and bipolar and related disorders in your patients: http://www.appi.org/Book/Subscription/JournalSubscription/id-3310/The_Pocket_Guide_to_the_DSM-5%C2%AE_Diagnostic_Exam.

In addition, many other excellent screening tools for these disorders can be found online at no cost at: http://www.integration.samhsa.gov/clinical-practice/screening-tools.

Suicide

Tragically, depressive and bipolar disorders often lead to suicide, making them potentially fatal illnesses if left untreated. One large analysis of 40 separate postmortem studies found that 45% of those who died by suicide had seen a primary care provider within the month before their death, and 77% had such contact within the past year [9]. Older adults who died by suicide were even more likely to have had recent contact with a primary care provider. Hence, it is extremely important to ask depressed and bipolar patients about suicidal intent. It should be noted that asking about suicidal ideation does *not* increase the risk of suicide. The SAD PERSONS screen assesses risk factors for suicide (S = Sex-male, A = age > 60, D = depression, P = previous

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attempt, E = ethanol/other drug abuse, R = rational thinking (loss of), S = suicide in family, O = organized plan/access, N = no support, S = sickness (chronic pain/disease)). The Columbia Suicide Severity Rating Scale is another excellent resource: http://www.integration.samhsa.gov/clinical-practice/Columbia_Suicide_Severity_Rating_Scale.pdf.

Newer approaches for assessing suicide risk are also rapidly emerging, such as a mobile application for Apple and Android devices, "Suicide Safe," from the Substance Abuse and Mental Health Services Administration (SAMHSA) website http://store.samhsa.gov/apps/suicidesafe/ and a blood test which may predict suicidal behaviors by examining certain combined epigenetic and genetic biomarkers [10] among others.

Differential Diagnosis

Detection and treatment of mood symptoms depends on properly identifying the potential etiology underlying the presenting complaint. Non-psychiatric conditions that can give rise to mood symptoms include environmental triggers, neurologic disorders, other psychiatric disorders, and medical comorbidity. Potential medical causes are diverse ranging from cardiovascular disorders to nutritional deficiencies. Psychosocial stressors may contribute to the acute onset of mood symptoms with major life changes or bereavement causing adjustment difficulties. Cognitive disorders, such as the neurodegenerative disorders, may present early in their course with noticeable alterations in mood. Excluding organic causes of depression to a reasonable degree of certainty is always the first step in making a diagnosis.

Substance use, personality, anxiety, and the somatoform disorders can all have an impairing mood component as a hallmark of their pathology. Treatment would include addressing the specific concerns in these populations such as assisting with the withdrawal syndrome, detoxification, and maintenance of abstinence in the patient with a substance use disorder.

Bereavement may present with symptoms consistent with depression. The DSM-5 removed the bereavement exclusion from its criteria, as many individuals may develop depression after a loss. Studies suggest that if treated promptly, symptom presence would be shorter. For this reason, if symptoms of a full, major depressive episode are present following bereavement, clinical judgment should be exercised to determine if the patient requires treatment. A preponderance of data support treating those meeting criteria for a major depressive disorder during the period of 2–12 weeks following bereavement [11].

Treatment Principles

The primary goal for the treatment of depression in the primary care setting is complete remission of depressive symptoms. The primary care clinician must allow an adequate trial of each medication before determining if the patient has failed that particular medication. An adequate trial includes sufficient length of time for the medications to demonstrate a response, which can be as early as 1–2 weeks in eventual responders to greater than 4 weeks in some individuals [12]. Obtaining measurements of response with the use of screening instruments to monitor response and progression toward remission may be beneficial in enhancing the quality of care and clinical outcome for patients. The PHQ-9, mentioned earlier in this chapter, and the Hamilton Rating Scale for Depression (HAM-D) are examples of a self-rated and a clinician-rated scale, respectively.

The primary care physician will be able to provide successful care to a bipolar patient depending on various elements such as illness severity, comorbidities, personal experience, ancillary support from the institution where the physician is practicing, and complexity of the case. Primary care physicians need to decide which level of care will be required; for example, would acute or long-term treatment be provided by them, or would a psychiatrist need to be involved through a referral or collaborative care?

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For most patients, acute and maintenance treatment will require pharmacological management. The objective of providing acute treatment is to reduce symptoms with adequate safety, making sure the medication is well tolerated. Monotherapy is commonly the first line of treatment, but many times, combination therapy will be required to manage the symptoms of bipolar disorder.

A word should be said about new trends in pharmacogenetic testing to ascertain response to antidepressant treatment. The following is a summary from an excellent article by Zeier and colleagues on this topic [12]:

> Substantial investigations of genomic sequencing have been devoted to identifying gene-drug interactions affecting response to antidepressant treatment. Individual responses to antidepressants, as well as the unpredictability of adverse side effects, leave clinicians with a prescribing strategy that often relies on trial and error. There are available pharmacogenetic testing products that are marketed to physicians. These tools use algorithms to integrate multiple genetic variants and assemble the results into an easily interpretable report to guide prescribing of antidepressants and other psychotropic medications. At present, there is insufficient data to support the widespread use of these pharmacogenetic tests in clinical practice. In some clinical situations, the technology may be informative, particularly in predicting side effects [12].

Treatment

Biologic Therapies

Depressive Disorders

Many pharmacologic agents are used to treat depressive symptoms including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). The clinician must make several decisions before recommending a specific antidepressant. Which medication will target the depressive symptoms with fewest side effects will need to be determined. Access to the medications (insurance formularies), their cost, and the ease of dosing will play an important part in the implementation of a treatment protocol.

Selective Serotonin Reuptake Inhibitors

The SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vortioxetine) are first-line agents in the treatment of major depressive disorder. Well-tolerated by many, these medications are widely prescribed for many psychiatric disorders. Physicians who have experienced using these medications will anticipate and use potential side effects to their advantage such as using a sedating medication with a patient with complaints of insomnia [13]. See Table 1 for further useful information on this topic.

The interactions of SSRIs with other medications will be important for the treating clinician to monitor on a continual basis. Constant surveillance is important for patient safety, as well as education about the signs/symptoms of toxicity secondary to their use of an antidepressant [14].

Serotonin-Norepinephrine Reuptake Inhibitors

The SNRI medications (desvenlafaxine, duloxetine, levomilnacipran, and venlafaxine) are used to treat depressive symptoms in refractory cases, as part of an augmentation strategy with an SSRI. They are also used as monotherapy if patients have a partial or nonresponse to an SSRI. Many clinicians believe that the SNRIs can be helpful in patients with comorbid anxiety and pain syndromes.

Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

The TCAs (amitriptyline, desipramine, doxepin, imipramine, nortriptyline, and protriptyline) and MAOIs (isocarboxazid, phenelzine, selegiline, tranylcypromine) are still widely used because of the wealth of data on their use, low cost, and effectiveness. Their higher incidence of side effects when compared to newer agents and their higher lethality in overdose have relegated these agents to a second-line use in most treatment plans when first-line medications have failed [15].

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Table 1 Indications for selected antidepressants

Antidepressant	Anxiety	Panic disorder	Sleep disorder	OCD	Pain	Fibromyalgia	Fatigued	Extra
SSRI								
Citalopram (Celexa)	+			+				Off label: GAD, binge eating, alcoholism, hot flashes, PMDD
Escitalopram (Lexapro)	+			+				
Fluoxetine (Prozac)		+		+		+	+	PMDD, bulimia, off label: Hot flashes, Raynaud's migraine *assoc., w/weight loss
Paroxetine (Paxil)	+	+		+				Social phobia, stuttering, PMDD *causes most sex dysfunction, orthostatic hypotension, and weight gain from SSRIs
Sertraline (Zoloft)	+	+		+				PMDD, off label: Pruritis *most GI upset from SSRIs
Fluvoxamine		+		+				PTSD, social phobia
SNRI								*can all cause insomnia/ agitation and sexual dysfunction
Venlafaxine (Effexor)	+	+					+	
Desvenlafaxine (Pristiq)								Venlafaxine works the same and is cheaper
Duloxetine (Cymbalta)	+				+	+		
Atypicals								
Bupropion (Wellbutrin)								Appetite suppressant, smoking cessation, few sexual side effects, seasonal affective disorder, ADHD (off label)

(continued)

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Table 1 (continued)

Antidepressant	Anxiety	Panic disorder	Sleep disorder	OCD	Pain	Fibromyalgia	Fatigued	Extra
Trazodone (Oleptro)			+					Off label: Aggressive behavior, etoh withdrawal, prevention of migraine
Mirtazapine (Remeron)			+					Off label: PTSD, hot flashes *associated with weight increase
TCAs								*beware of long QT, EPS, agranulocytosis *sex dyfxn -contraindicated in older patients, hypotensive patients, or heart-diseased patients
Amitriptyline					+			Off label: Postherpetic neuralgia, migraine prophylaxis, eating disorder *assoc. w/wt gain, anticholinergic SE
Clomipramine				+				Off label: Premature ejaculation *assoc. w/wt gain, anticholinergic side effects
Doxepin	+	+						*assoc. w/wt gain
Imipramine				*				Pediatric-nocturnal enuresis *assoc. w/wt gain
Trimipramine								*assoc. w/wt gain
Desipramine							+	Off label: Postherpetic neuralgia, vulvodynia, eating disorder *assoc. w/weight loss

(continued)

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Table 1 (continued)

Antidepressant	Anxiety	Panic disorder	Sleep disorder	OCD	Pain	Fibromyalgia	Fatigued	Extra
Nortriptyline								Off label: Chronic urticarial, angioedema, pruritis, smoking cessation, ADHD, postherpetic neuralgia

Warning:
· Paxil – do not take in first trimester of pregnancy; associated with birth defects
· Prozac – neonatal persistent pulmonary htn >20 weeks gestation, neonatal serotonin syndrome 3rd trimester, growth suppression in pediatric patients
TCAs – order EKG first to look for long QT
2014 Lillian Sarfati, MD. In Allespach H, Sarfati L, "DSMS: Depressive, Bipolar & Related Disorders (What You Need to Know Now)." 2014 AAFP Scientific Assembly Washington, DC

Other Antidepressants

Antidepressants with different mechanisms of action from the SSRIs/SNRIs (bupropion, mirtazapine, trazodone, and vilazodone) are also widely prescribed. Bupropion is often used to augment other antidepressants or as monotherapy to offset sexual side effects that may be experienced during treatment for depression. Mirtazapine is often prescribed as an adjunct, or monotherapy, for patients with insomnia and/or anorexia. Trazodone is another agent that is widely used for insomnia, even more so than for its antidepressive qualities [15]. The S-enantiomer of ketamine, esketamine, was recently approved for treatment-resistant depression [16]. A list of medications currently approved for treating major depressive disorder is below (Table 2).

Augmentation

Partial response to pharmacotherapy is common in many patients. When a patient has an initial response to an antidepressant medication, with the dosage and treatment length being optimized, a plateauing effect may take place with stagnation in further improvement. Instead of switching to another medication in the same class, the physician may consider augmentation strategy. Augmentation of antidepressants, with other agents, has demonstrated efficacy in several circumstances, including being added to a regimen when a patient has partial response to treatment, the patient is unable to tolerate higher doses of the base antidepressant, or if switching to a different medication is not practical. Several medications are used in augmentation strategies for the treatment of depressive symptoms including mood stabilizers (i.e., lithium), atypical antipsychotics (i.e., aripiprazole), triiodothyronine, stimulants (i.e., modafinil), and hormone replacement (i.e., testosterone in men) [17].

Alternative/Complementary Options

Knowing about the use of alternative treatments by patients is of paramount importance to the treating physician. Understanding the potential interactions with other recommended therapies may guide the treatment plan. Data for the efficacy of substances such as St. John's wort, high-dose folate, omega-3 fatty acids, and S-adenosyl methionine (SAMe) are limited. Therefore, they cannot be recommended as first-line options [18]. Therapeutic massage, physical exercise, meditation, and acupuncture/acupressure are also widely used with good effect but limited evidence [18].

Bipolar and Related Disorders

Management of bipolar disorder varies according to the current presentation of the patient, and it should be tailored to either acute or maintenance

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Table 2 FDA-approved medications for major depressive disorders [17]

Medication	Dose range	Half-life	Considerations
Amitriptyline (TCA)	10–300 mg	10–28 h	Substrate for CYP450 2D6, 1A2
Bupropion (other)	75–450 mg, depends on formulation	4–10 h parent; active metabolite 20–27 h	Multiple formulations: Immediate release (IR), sustained release (SR), extended release (XL). Inhibits CYP450 2D6
Citalopram (SSRI)	10–40 mg, 10–20 mg if >60yo	23–45 h	Weak inhibitor of CYP450 2D6
Desipramine (TCA)	10–300 mg	24 h	Substrate for CYP450 2D6, 1A2
Desvenlafaxine (SNRI)	50–400 mg	9–13 h	Minimally metabolized by CYP450 3A4
Doxepin (TCA)	1–6 mg	8–24 h	Substrate for CYP450 2D6
Duloxetine (SNRI)	20–60 mg	12 h	Substrate for CYP450 2D6, 1A2
Escitalopram (SSRI)	5–20 mg	27–32 h	No significant CYP450 interactions
Fluoxetine (SSRI)	10–80 mg	2–3 days for parent drug, active metabolite 2 weeks	Inhibits CYP450 2D6, 3A4
Imipramine (TCA)	10–300 mg		Substrate for CYP450 2D6, 1A2
Isocarboxazid (MAOI)	10–40 mg	Up to 21 days	Significant interactions with other drugs that block serotonin reuptake
Levomilnacipran (SNRI)	20–120 mg	12 h	Substrate for CYP450 3A4
Mirtazapine (other)	7.5–45 mg	20–40 h	No significant CYP450 interactions
Nortriptyline (TCA)	10–150 mg	36 h	Substrate for CYP450 2D6
Paroxetine (SSRI)	10–60 mg	24 h	Inhibits CYP450 2D6
Phenelzine (MAOI)	15–90 mg	Up to 21 days	Significant interactions with other drugs that block serotonin reuptake
Protriptyline (TCA)	10–60 mg	74 h	Substrate for CYP450 2D6
Selegiline (MAOI)	6–12 mg/24 h	18–25 h	Transdermal patch used for depression
Sertraline (SSRI)	25–200 mg	22–36 h parent drug; 62–104 h for metabolite	Inhibits CYP450 2D6, 3A4
Tranylcypromine (MAOI)	10–40 mg	Clinical action up to 21 days	Significant interactions with other drugs that block serotonin reuptake
Trazodone (other)	50–600 mg	Biphasic half-life: 1st phase 3–6 h, 2nd phase 5–9 h	Substrate for CYP450 3A4
Venlafaxine (SSRI)	(IR) 37.5–375 mg; (XR) 37.5–225 mg	3–7 h parent drug; 9–13 h for metabolite	Immediate release, extended release formulations
Vilazodone (other)	10–40 mg	25 h	Substrate for CYP450 3A4
Vortioxetine (SSRI)	5–20 mg	66 h	Substrate for CYP450 2D6

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Table 3 FDA-approved treatments for bipolar disorder [19, 20]

Acute mania	Acute bipolar depression	Bipolar maintenance
Lithium	Olanzapine/fluoxetine	Lithium
Chlorpromazine	Quetiapine, XR	Lamotrigine
Valproic acid, ER	Lurasidone[a]	Olanzapine
Olanzapine[a]	Cariprazine	Aripiprazole[a]
Risperidone[a]		Quetiapine, XR (adjunct)
Quetiapine, XR[a]		Risperidone long-acting injection[a]
Ziprasidone		Ziprasidone (adjunct)
Aripiprazole[a]		
Carbamazepine, ECR		
Asenapine[a]		
Cariprazine		

[a]Adjunctive and monotherapy. ER, ERC, XR: extended release formulations

treatment. Both phases of the illness may entail depressive or manic symptoms, and this will determine the appropriate intervention to choose (please refer to list below) (Table 3).

Acute Treatment

Mania. The goal of treatment of a manic episode is to achieve rapid relief of symptoms resulting in full remission in a safe setting. Most often, hospitalization during a manic episode is required in order to maximize patient safety. Pharmacologic therapy is the cornerstone of treatment for a manic episode, and monotherapy can be implemented using mood stabilizers or antipsychotic agents. The FDA-approved mood stabilizers include lithium, valproic acid, and carbamazepine. Lithium should be titrated slowly to prevent toxicity and is associated with moderate improvement of symptoms in 40–80% of patients after 2–3 weeks of treatment [21]. Valproic acid and carbamazepine have similar efficacy in decreasing symptoms as lithium but have a more rapid onset of action. Over 50% of patients treated with these two medications experience improvement in their manic symptoms.

Of the first-generation antipsychotics, only chlorpromazine has been FDA approved to treat acute mania. Due to frequent side effects, second-generation antipsychotics are used more often. Of the second-generation antipsychotics, risperidone, quetiapine, ziprasidone, aripiprazole, and asenapine have been approved for use as monotherapy in acute mania. All of them, except for ziprasidone, have also been approved for use as adjunctive treatments to mood stabilizers. Attention should be directed to the development of akathisia, somnolence, weight gain, and other extrapyramidal symptoms such as tardive dyskinesia when using these agents.

Depression. Only four agents have been approved for the treatment of bipolar depression. These include olanzapine + fluoxetine combination, quetiapine and quetiapine XR, lurasidone, and cariprazine. Of these, only quetiapine is approved to treat acute depression in patients suffering from bipolar II [22] and, along with cariprazine, is approved as monotherapy to treat manic episodes.

Although the use of antidepressant medications may seem the appropriate choice for treating depression in patients with bipolar disorder, there is scarce evidence for their use in the literature, with randomized controlled trials showing that antidepressants are not better than placebo in this situation [23], and they may precipitate mania or hypomania if used as monotherapy.

Mixed States. When patients meet criteria for mixed features, valproic acid is a good choice for treatment. Lithium has not shown benefit with this presentation or during rapid cycling and should be avoided.

Maintenance Treatment

Depression

In terms of unipolar depression, a general rule of thumb is that once a patient has been asymptomatic for 6 months to a year, continue to treat for 12 months for those who have had one episode of

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major depression, 2–3 years for those patients with two episodes of major depression, and consider lifetime maintenance treatment with antidepressants for individuals who have experienced three or more major depressive episodes in their lives.

Bipolar Disorder

For bipolar disorders, after an acute episode has been controlled, maintenance treatment should be implemented to prevent recurrence of symptoms, and the current recommendation is to continue lifelong treatment. Only two mood stabilizers are approved as monotherapy for maintenance in bipolar disorder: lithium and lamotrigine. Lamotrigine has been shown to prevent recurrence of depressive symptoms but has been linked to Stevens-Johnson syndrome. Monitoring for the development of a rash is advised. Lithium has proven to decrease the incidence of suicide but has been linked to many side effects, including renal and thyroid problems and teratogenicity. Lithium blood levels should be monitored carefully, and close attention should be given to medication interactions, as it has a very narrow therapeutic index.

While no medications have been approved to treat cyclothymic disorder, mood stabilizers may be considered on a case-by-case basis.

In addition to mood stabilizers, 5 second-generation antipsychotics have also received approval for treatment: olanzapine monotherapy, aripiprazole monotherapy and adjunctive treatment, quetiapine adjunctive treatment, risperidone long-acting injectable monotherapy and adjunctive treatment, and ziprasidone as adjunctive treatment. It is important to mention that if the primary care physician does not have experience or does not feel comfortable using any of these medications for the treatment of bipolar disorder, they should defer the care of the patient to a more experienced provider.

Psychological Therapies

In the past 40 years, 400 randomized controlled trials have investigated the beneficial effects of psychotherapies for adult depression. These modalities include cognitive-behavioral and interpersonal therapies and newer approaches, such as acceptance and commitment therapy and cognitive bias modification. It appears all of these therapies are equally effective, and a growing number of studies are focused on scaling up of psychological services, including the training of lay counselors, telephone-based psychotherapies, and Internet-based counseling [24]. It should be noted that medication therapy may not be the optimal choice for many patients with depression. Specifically, for patients with mild to moderate symptoms who do not exhibit severe impairments in overall functioning, psychotherapy may be more efficacious than pharmacologic treatment and should be considered as a first-line recommendation.

For individuals with bipolar disorders, psychoeducation focusing on the recognition of early warning signs of relapse appears to be an effective adjunct to medication management. Cognitive-behavioral therapy, family-focused therapy, and interpersonal therapy have also been found to be particularly efficacious when used as adjuncts to pharmacotherapy to improve both symptoms and overall function [22].

Physician-Administered Counseling Strategies

Family physicians are in an excellent position to teach patients selected cognitive-behavioral interventions, such as cognitive restructuring. This can be accomplished by simply teaching patients that their distorted, negative, reactive thoughts create distressful feelings (such as depression and anxiety) which, in turn, lead to increased pain and other uncomfortable somatic symptoms and subsequently to unhealthy and maladaptive behaviors. Cognitive restructuring consists of asking the patient, "What can you tell yourself. . .or what would the wise, rational, nonreactive part of you tell you to make you feel less distressed (e.g., angry, sad, anxious, etc.)?" [25]. The patient may be given "homework" to practice changing thoughts to change feelings and then asked about their success or struggles in doing this exercise at each visit. Other counseling techniques which family physicians can successfully implement in an office-based setting with depressed and bipolar patients include brief mindfulness and diaphragmatic breathing exercises [25].

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Other Non-pharmacological Interventions

Electroconvulsive therapy (ECT) is a well-documented and effective treatment for major depressive and bipolar disorder. It remains the gold standard of treatment for refractory depressive disorders and should be considered a first-line treatment for major depressive disorder presenting with catatonia, severe suicidality, severe psychosis or agitation, peripartum depression, and situations where a rapid response to treatment is required. For bipolar disorder, benefit has been demonstrated in studies of patients in both manic and depressive states of their illness [26].

Deep brain stimulation (DBS) is a newer intervention designed to reduce depressive symptoms but is limited to specific clinical settings and will benefit from more data on its efficacy [27]. Vagal nerve stimulation (VNS) is usually reserved for treatment-refractory cases but has no positive RCTs proving its efficacy [14]. Repetitive transcranial magnetic stimulation (rTMS) was approved by the FDA in 2008 to treat major depressive disorder in patients who failed one, but no more than two standard antidepressant trials. rTMS involves creating a powerful electrical current near the scalp delivered by repetitive pulses (microseconds) of an MRI-strength (close to 1.5 Tesla) magnetic field from a coil placed over the scalp. Sessions usually last 20–40 min, 5 days a week, typically for 6 weeks. This procedure is carried out while the patient is awake, resting in a specially equipped chair. More research is needed to test the efficacy and safety of this procedure in patients with bipolar disorder.

Light therapy is effective for the treatment of seasonal affective disorders [18].

Social Treatments

As discussed throughout, depressive and bipolar disorders can have a catastrophic impact on interpersonal, occupational, and physical functioning. However, patients should be made aware that these illnesses can be treated to remission and that their family physician will be there to support them throughout. It is important to involve social work as needed and to inquire about other support networks. By its nature, depression – whether unipolar or bipolar – is an extremely isolating illness, and every attempt should be made to engage patients in available resources, such as local or online support groups, twelve-step programs (e.g., Emotions Anonymous: http://www.emotionsanonymous.org/), and organizations such as the Depression and Bipolar Support Alliance http://www.dbsalliance.org/site/PageServer?pagename=home.

Opiate Use in Depressed Patients

The use of opiates is commonly seen in patients with chronic pain. There has been a well-established relationship between chronic pain, depression, and long-term use of opiates. Even with the use of antidepressants, many of these patients will not achieve adequate response to treatment because of their use of opioids. The use of buprenorphine, an opioid partial agonist, has been an effective tool in the primary care setting for medication-assisted treatment (MAT) by physicians who have completed training and who have met the certification requirements to prescribe this medication. Studies are still ongoing which use buprenorphine as adjunctive treatment to depression, as this medication has been shown to improve mood and satiate cravings for opiate use [28].

Special Populations

Children and Adolescents

A conservative approach is usually best with individual, group, or family therapy being the first treatment modality, adding in pharmacotherapy for the treatment-resistant or severe cases. It is recommended that when treating children and teens with depression and bipolar disorder, a child psychiatrist should be consulted early on; however, if this is not possible, caution with prescribing in these populations should be observed, as many psychotropic medications are not FDA

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approved for use in children. Children and adolescents differ in their pharmacokinetics from adults and require special consideration when diagnosing and treating mood disorders. Children can present with more irritability and somatic complaints than concerns about their depressed mood. Children tend to have a faster elimination rate for medications because of their greater liver/kidney parenchyma to body size, increased body water, and decreased amount of adipose tissue [29]. This faster rate of clearance means that a steady state is reached sooner, but the medications may require more frequent dosing to maintain the steady state. In addition, when prescribing antidepressants for children/teens, parents/caregivers should be given medication guides which discuss the potential warning signs of these medications. These guides are available at: http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm096273.htm.

Older Adults

Older individuals may have confounding manifestations of other medical conditions that may resemble depression, including fatigue, decreased energy, decreased appetite, or psychomotor retardation. For this reason, a careful look should be taken to each individual case to discern between those symptoms caused by depression and those caused by a medical problem. A depression screening form especially tailored for older adults is the Geriatric Depression Scale (GDS) which may be more accurate for this population. It is important to note that depression is not a normal part of aging and it should be treated accordingly. Older adults that are diagnosed with depression at a later age for the first time should be treated at least for 2 years before treatment tapering is considered, in order to decrease the risk of recurrence.

It is important, when assessing older adults, to understand that medical and neurological comorbidities may confound recognition of the clinical features of bipolar disorder as well. It has been reported that elderly persons with bipolar disorder suffer from more medical illnesses than those without bipolar disorder [30]. These include cardiovascular disease, hypertension, type II diabetes, and obesity. Treatment considerations include minimizing or avoiding the use of medications that have anticholinergic properties, as these may affect the elderly individual by causing dry mouth, blurry vision, constipation, urinary retention, hypotension, tachycardia, cognitive impairment, and delirium. For depression and bipolar disorder, medications are generally started at half the dose that would be recommended for a younger adult and should be increased more slowly by half the recommended dose.

Pregnant and Lactating Women

The antenatal and postnatal periods are particularly vulnerable times for depression to impact the functioning of the mother. Untreated/undertreated antenatal depression is associated with a plethora of adverse outcomes including premature delivery, low infant birth weight, higher risk for developmental delay in the child, and decreased likelihood of breastfeeding initiation [31]. Postpartum depression is associated with impairment in the mother-infant attachment. Treatment is guided by risk versus benefit, with detection of depression as early as possible in the pregnancy. The decision of which antidepressant to recommend to the pregnant patient will depend on many factors including previous response to treatment and severity of illness. Like most of the antidepressants, sertraline has a “C” classification for safety in pregnancy and may be continued during breastfeeding. Sertraline and paroxetine are the preferred first-line choices for lactating women secondary to their safety profile when compared to the other antidepressants [32]. Paroxetine has a “D” classification for safety in pregnancy and should be avoided in the first trimester.

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The Suicidal Patient

33

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General Principles

Definition/Background

Suicide is the intentional ending of one's own life that is oftentimes the end result of another pathologic process such as substance abuse, mood disorders, or psychosis. Suicidality itself may be divided into a continuum of seriousness ranging from thoughts of death to passive and then active

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suicidal ideations which range from formulation of a plan, to suicide attempts, and finally to completed suicide [1]. A related though somewhat separate entity is chronic suicidality often seen in the context of personality disorders [2, 3].

Epidemiology

In 2017, suicide was the 10th leading cause of death in the United States, accounting for the loss of more than 47,000 lives. In the 10–44 age group, it was second only to unintentional injury as a cause of mortality. Suicide drops out of the top 10 causes of death only in the group of people 65 and older, though the absolute number remains high [4].

Suicide rates vary by age, race, and gender. Teens and those in the fourth decade of life are the most likely to die by suicide. Females are twice as likely to attempt suicide, while males are four times more likely to be successful in an attempt. White Americans attempt suicide at 10 times the rate of African-Americans or Pacific Islanders, while Native Americans have roughly twice the rate of other minority groups [5]. Groups that perceive themselves to be socially isolated, such as sexual minorities, are also at increased risk [6].

Approach to the Patient

Assessment of suicide risk is a clinical decision that can only be made after a comprehensive evaluation. In 2014, the United States Preventive Services Task Force reiterated their previous I-statement regarding routine screening for suicide risk in the primary care setting, given insufficient evidence to evaluate benefit versus harm. However, this recommendation is only for the screening of asymptomatic persons [7]. Nearly half of the patients who die by suicide have seen a healthcare clinician in the preceding month [8]. Physicians should therefore remain alert for suicidal ideation among their patients, particularly among those with risk factors that are discussed below.

Diagnosis

History

Historical information may be divided into risk factors that increase the likelihood of a suicide attempt, while protective factors decrease the relative risk.

Risk Factors

Risk factors for suicide include biological, environmental, psychiatric, and social factors, though there is considerable overlap between categories. A general list of risk factors may be found in Table 1. Several risk factors deserve particular attention because of their significance. Despite psychiatric treatment, patients who have made a previous suicide attempt are at significantly increased risk for the remainder of their lives. In the year following an attempt, these patients are 100 times more likely to die by suicide than members of the general population [9]. Psychiatric disorders, especially depression with anhedonia and/or anxiety, bipolar disorder

Table 1 Risk factors for suicide [10, 12]

Biological and cultural
Male gender
Caucasian, Native American, Native Alaskan
Late adolescence, or age >60 years
Family history of suicide
Major illness or chronic disease, including chronic pain
Environmental
Recent loss of loved one
Access to means (such as firearms)
Exposure to suicide
Unemployment, or other financial stressors
Social stressors including isolation, recent humiliation, or debt
Psychiatric
Depression esp. with comorbid anxiety disorders
Bipolar disorder, esp. mixed episodes
Personality disorder
Schizophrenia, esp. with command hallucinations
Hopelessness, anhedonia
Other psychoses
Substance use disorder
Previous suicide attempt
Social
Social isolation
Never married, widowed, or divorced

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with a mixed episode, and personality disorders, also confer a significantly increased risk [10]. Finally, any patient with a known or suspected substance use disorder should receive special attention during episodes of depression, stress, or following stated suicidal ideation [11]. Substances are believed to contribute to suicide risk either by enabling actions the victim may otherwise be unable or too afraid to take or by their effects of impairing judgment, increasing impulsivity, and worsening depressive symptoms.

Protective Factors

There are a variety of protective factors that decrease the likelihood of suicidal behavior. These include access to healthcare, the availability of psychological treatment, a sense of being connected to family and community, being married, and cultural and religious beliefs that oppose suicide. Each of these factors provides a reason for continued living and offers hope that the symptoms of depression will improve.

Laboratory and Imaging

Laboratory and imaging orders may be considered to diagnose or exclude possible medical conditions that could be contributing to the presenting complaint of suicidal ideation. For example, obtaining a urine drug screen and blood ethanol level may be helpful in determining further risk for suicide due to impaired judgment, confirm or refute elements of the differential diagnosis such as substance dependence, and provide guidance on treatment options [13].

Special Testing

There are no validated clinical decision-making tools to assess suicide risk as the interplay of the various risk and protective factors is complex [14]. Many physicians fear inquiring about suicidal thoughts, even among patients who are known to be at high risk. This is due, at least in part, to a belief that by asking the physician may actually cause the patient to consider suicide; in fact studies have shown the opposite to be true. Patients are not more likely to make a suicide attempt if asked about ideation. In fact, many are actually relieved that their physician has inquired about a topic that they may have been too afraid to broach [15]. Direct inquiry about suicidal thoughts has also been associated with improved identification of those at risk for suicide [16]. Physicians should be alert for patients at risk for suicide and should not hesitate to discuss suicidal thoughts with their patients.

Treatment

Behavioral

When evaluating a patient who is experiencing suicidal ideation, the primary care physician must determine where the patient is on a spectrum of risk for completing suicide. According to the US Preventive Service Task Force recommendation statement, the assessment for risk of suicide is complicated by the fact that individual risk factors alone provide little predictive value about whether or not an individual will complete suicide [7, 17]. Furthermore, there is a paucity of data on what specific components should be included in a risk assessment in order to reliably predict suicide [17]. Therefore, a two-step process to guide physicians in evaluating patients who are at risk for suicide has been developed: the suicide risk assessment and the suicide risk formulation [13].

In a suicide risk assessment, information is gathered from the patient that may include general medical history, history of suicide attempts, any current or previous mental health diagnoses or treatment, family history, current symptoms, observed behaviors, information from family and associates, mental health screening tools, and the medical record. The use of alcohol, illicit substances, prescription medication abuse, and other psychosocial stressors (such as potential loss or recent loss of employment, divorce, recent diagnosis of terminal illness) should also be assessed. The assessment of suicidal ideation may include

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inquiries into the specificity of plan, lethality of the plan, and access to means. Additionally, a review of protective factors (i.e., resources available to the patient that tend to be protective against suicide), such as social support, religious beliefs, dependent children, willingness to seek help, is important. This information then can be synthesized for the suicide risk formulation [13, 14, 18]. The more information that is gathered in the suicide risk assessment, the better the physician will be able to estimate the patient's level of risk [14]. While there are no standard assessment questions, some questions physicians can consider within the suicide risk assessment are whether the patient has had recent or current thoughts of self-harm or death, if there is a plan to engage in self-harm, do they have access to method(s), is there intention to follow through with the plan, if there have been past attempts, if there is a family mental health history, and what has kept them from engaging in self-harm [19, 20].

There is no particular guideline to help physicians prepare the suicide risk formulation, but rather the physician considers the additive interaction of all of the risk factors for a particular patient. Regarding risk level, the physician can consider whether a patient is at acute or chronic risk. Within the acute and chronic categories, the physician must then determine whether the risk is low, intermediate, or high [2] (see Table 2).

Following placement into a risk category, the physician can develop an appropriate treatment plan. For patients at high risk, treatment may be inpatient hospitalization for stabilization. Clinicians should have a plan in place for notification of emergency transport in an efficient manner, thereby reducing unnecessary patient waiting time or leaving against medical advice. The patient should be directly monitored until emergency services arrive. If the patient refuses inpatient hospitalization, involuntary admission or commitment may be required [2]. Laws for involuntary commitment differ among states and jurisdictions.

Patients who are assessed to be in the acute but intermediate-risk category may be more challenging when developing a treatment plan. These patients may be offered inpatient hospitalization for monitoring and medication stabilization. However, they may refuse inpatient treatment as an option and may not be suitable to involuntary hospitalization due to the lack of current intent to engage in self-harm, have certain protective factors, and/or are able and willing to comply with an outpatient treatment plan. The outpatient treatment plan for these patients should be comprehensive and include a suicide safety plan, close follow-up with the specific goal of reassessment of suicidal ideation, and provision of emergency resources, such as the suicide crisis hotline, restricted access to means of self-harm, and inclusion of family/friends if possible (see Table 3). The suicide safety plan should be given to the patient and/or family members, if present, in order to ensure that the patient can refer back to

Table 2 Risk categories for suicide [2, 18]

Acute	
High risk	May include ideation with intent and/or serious risk factors that impair judgment
Intermediate risk	May have ideation and a collection of risk factors but lacks current intent
Low risk	No plan, intent, or behaviors indicating preparation for suicide
	May have had ideation but there are also protective factors present
Chronic	
High risk	Chronic mental health concerns that are uncontrolled
	Absent protective factors
	Unpredictable social stressors (relationship problems, job losses, lower socioeconomic status)
Intermediate risk	Have chronic mental health or health conditions that vacillate in stability but have protective factors and/or coping skills
Low risk	Have a history of mental health concerns but have protective factors/coping resources

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Table 3 Suicide safety plan components [21]

A list of coping skills/strategies that one can use to decrease symptoms. For example, the patient could generate a list of calming activities or hobbies that are enjoyable and accessible, make a list of reasons for not engaging in self-harm, and/or make a list of positive qualities, etc.	Warning signs that symptoms are worsening or symptoms to monitor such as an increase in suicidal thoughts, depressive symptoms, progression to making a plan for how to commit self-harm, increased isolation, substance use
List of resources such as crisis hotlines	Elicit any other resources that the patient might feel are helpful
Removal of items that may be used to cause self-harm	A list of social support resources (friends or family)

the steps they need to take should their symptoms worsen and require intensive intervention. A referral to psychiatry and/or therapy services might be advantageous for the patient as these specialties have access to resources and treatment options that may be unavailable to primary care physicians [2, 21].

Patients who are considered at lower risk may be described as individuals who have suicidal ideation without a plan or intent and have protective factors, and there is confidence that the patient will seek services if their symptoms increase.

There are patients who are at chronic risk for suicide due to persistent mental and/or medical illness, personality disorders, impulsivity, and engagement in substance abuse or dependence, those who have persistent psychosocial stressors, and/or those who have poor coping and problem solving skills. Treatment strategies for patients who are at higher and intermediate chronic risk include ensuring that they maintain follow-up in specialty care, are compliant with their current treatment plan, and have access to a specified suicide safety plan. Patients who are at low chronic risk may have adequate coping skills, social support, and other resources. These patients may benefit from preventive strategies such as monitoring their psychosocial environment for stressors and reiterating the availability of resources if needed [2].

Medication

The treatment plan for suicidal ideation may include initiation of medication with additional safety planning and plans for follow-up. Specialty services such as therapy and/or psychiatry consultation may also be offered [2]. If a selective serotonin reuptake inhibitor (SSRI) is initiated, the Food and Drug Administration (FDA) issued a black box warning that these medications may increase the presence of suicidal thoughts or actions during initiation of these medications in children and adults ages 18–25. However, it is important to remember that depression and other serious psychiatric illnesses are the strongest risk factors for suicide. Careful consideration of the benefit-risk ratio, detailed counseling, and close monitoring and follow-up of any patient thought to be at risk for suicide are central to management. Furthermore, other medications that hold potential for overdose or toxicity should be limited or monitored.

Prevention

Identification

Given the irreversible nature of completed suicide, prevention is of utmost importance; identification of patients at risk prior to an attempt is key. Primary care physicians must be alert for patients at risk for suicide. Those who commit suicide are likely to have been evaluated by a primary care clinician in the 30 days preceding death [8]. However, the benefit of screening for suicide risk in primary care populations is uncertain [7].

Multiple barriers exist to the disclosure of suicidal intent. These include fear of stigmatization and invasion of privacy by strangers. Truthful disclosure is encouraged by maintaining a comfortable longitudinal relationship with a

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provider. In the absence of previously established rapport, suicide risk assessment (either via clinical assessment or screening tool) should be done in a manner that is personal, employing both a caring attitude and genuine concern. Routine assessment by ancillary staff should be avoided as this may be perceived as impersonal and disrespectful, possibly resulting in failure to disclose suicidal thoughts to staff or clinicians [22].

Though disclosure of suicidal intent has historically relied upon an interaction between a clinician and a patient, technological advances may allow digital phenotyping to identify at-risk individuals in the future [23]. Similarly, utilizing electronic health record data combined with self-report questionnaires could allow prediction of a suicide attempt as well [24].

General Considerations

In addition to identification of at-risk patients, several other strategies may be employed to prevent suicide and suicide attempts. Educating primary care physicians has been shown to decrease rates of suicide, and though evidence is less robust, gatekeeper training may also play a role in reduction of suicide [25]. Restricting access to lethal methods through detoxification of domestic gas, decreasing pesticide absorption as well as the restriction of their sale, and limiting access to certain medications (including packaging changes) have been effective in reducing suicide rates [25, 26]. In the United States, stricter firearms legislation, specifically, has been shown to decrease incidence of both pediatric and adult suicides; however, evidence of benefit is conflicting when implemented in other countries. Furthermore, installing barriers at common jumping sites has also been shown to reduce death by suicide [25]. Education of the general public is an important component of suicide prevention, serving to promote early identification and management of mental health conditions and to destigmatize mental illness [26]. Community-based programs that integrate these principles, as well as promoting a system-wide approach to suicide prevention and supporting the implementation of comprehensive policy changes, have been successful in reducing suicide rates [27, 28]. Furthermore, family-based interventions, specifically for suicidal adolescents, decrease suicidal ideation and risk [25], and risk for older adults may be mitigated by depression screening in combination with community follow-up [29]. School-based interventions can additionally impact suicidal ideation and attempts [30]. Media engagement in suicide prevention efforts can be accomplished through responsible reporting [26, 31]. The media can serve as a vehicle for public education on a large scale. However, imprudent media reporting also can potentially worsen suicide risk by inadvertently glamorizing suicide and by publicizing suicide hot spots that may attract vulnerable persons [25, 31]. However, the effectiveness of public awareness campaigns is uncertain [25].

Therapeutic Considerations

Several psychiatric disorders, including depression, are associated with an increased likelihood of suicide [10] (see Table 1). (To this end, the USPSTF recommends screening adolescents and adults for major depressive disorder (MDD) when adequate support systems and follow-up care are available [7].) Failure to optimize treatment of conditions such as depression contributes to many suicide attempts [26], and initiation of pharmacologic therapy with SSRIs or tricyclic antidepressants has been shown to reduce rates of attempted suicide [25].

Psychotherapy for suicide attempters including cognitive therapy and interpersonal psychotherapy plays a role in reducing suicide attempts [32, 33]. In adolescents, cognitive therapy is also effective in reducing suicidal ideation and behavior [25]. An additional psychotherapeutic modality, dialectical behavioral therapy, has also been shown to reduce suicide attempts, improve treatment adherence, and reduce utilization of healthcare resources in patients with borderline personality disorder [34]. Finally, electroconvulsive therapy, often a therapeutic last resort, quickly resolves suicidal thoughts; therefore, it has been proposed

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that this modality might be preemptively used more often [25].

Inpatient Considerations

Attempted and completed suicide by inpatients can be limited by several interventions. Ensuring a safe environment that is free of potential means as well as adequate and supportive supervision reduces suicide risk [35, 36]. The disruptive effect of impending environmental changes or transitions – e.g., discharge, staffing changes, and variation in personnel schedules – must also be minimized by ensuring quality staff communication [35].

Follow-Up Care

Post discharge follow-up contact plays an important role in decreasing suicide risk [37]. After a failed suicide attempt, ensuring timely and frequent follow-up care (especially after ER evaluation or hospital discharge) can extend the amount of time between discharge and a repeat suicide attempt, thus allowing possible intervention and prevention of adverse events [38] (see Fig. 1). In fact, suicide risk remains markedly elevated for years after an attempt; therefore, long-term prevention efforts must extend beyond the immediate post discharge time period [39]. Particularly for adolescents hospitalized for suicidality, utilizing technology-enhanced interventions after hospital discharge may play a role in decreasing suicide attempts [40].

Emerging Environmental and Other Considerations

Emerging evidence supports several non-traditional suicide risk factors. Altitude has been proposed as a potential risk factor for suicide, presumably due to metabolic stress as a result of hypoxia [41]. Among elderly patients, lack of quality sleep seems to confer an elevated risk of suicide regardless of the presence of a mood disorder [42]. Chronic medical conditions, such as pain, could confer an increased risk of suicide. In fact, chronic pain, irrespective of type, is an independent risk factor for suicide and is associated

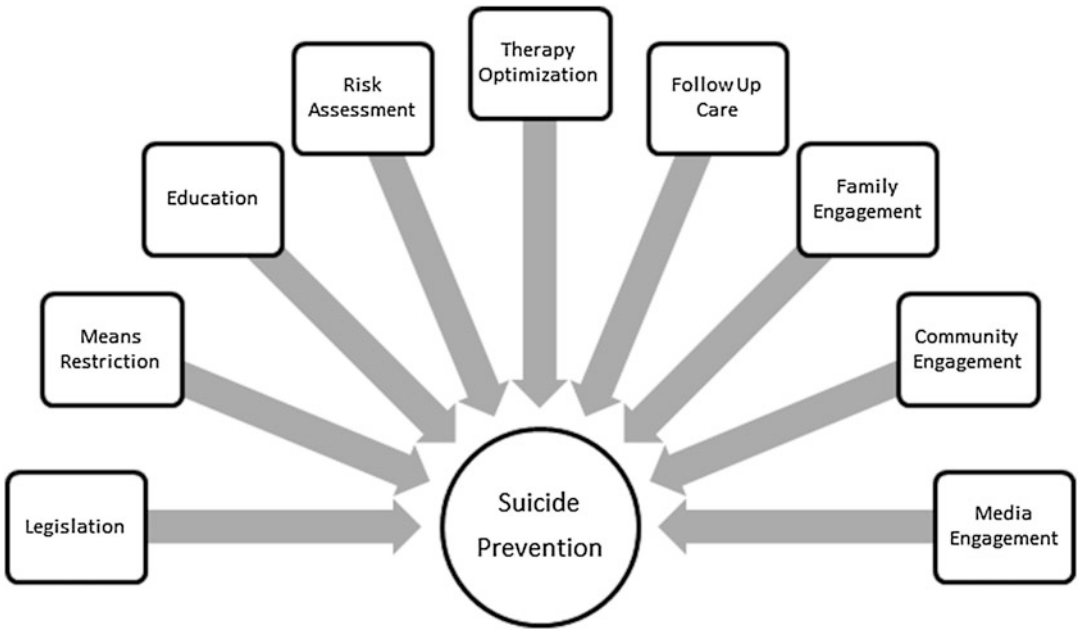


Fig. 1 Components of suicide prevention [20–22, 24, 25, 34]

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with a doubling of risk of suicidal thoughts as well as suicide completions [43]. Moreover, glucocorticoid therapy appears to increase the risk of attempted or completed suicide as well as utilization of hypnotic medications [44, 45]. Tobacco dependence and posttraumatic stress disorder (PTSD) are also emerging as risk factors for suicide [46]. Recent prison release seems to be associated with increased suicide risk especially in the presence of comorbid mental illness or substance abuse [47]. Future approaches aimed at mitigating suicide risk may include strategies to modify these risk factors.

Family and Community Issues

Child survivors of parental suicide are at increased risk of suicidal ideation and hospitalization for suicide attempts [34]. These children are also at risk for hospitalization related to depressive and anxiety disorders as well as other psychiatric symptoms and social maladjustment [48]. Children exposed to adverse experiences (e.g., domestic violence, divorce, a depressed or suicidal household member, or physical, sexual, or emotional abuse) are at increased risk of attempted suicide [49]. Of note, multilayered suicide prevention programs decrease the risk of moderate to severe family violence as well as overall risk for completed suicide [27, 28]. Finally, the lifetime economic burden of suicide is great, costing in billions of dollars due to medical costs and lost productivity [50].

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Somatic Symptom and Related Disorders

34

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General Principles

Introduction

Somatization is a term used to describe psychological or emotional distress manifesting in the form of physical symptoms. These complaints can be frequently seen in the primary care setting. Patients will often undergo significant medical testing to rule out organic causes. This testing can lead to unnecessary costs and potential harm.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5) defines Somatic

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Symptom and Related Disorders as the presence of physical symptoms and or excessive concern regarding medical illness or symptoms [1]. This is a change from the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-4), which previously categorized these disorders as Somatoform Disorders. Another change from DSM-4 to the DSM-5 is the recognition that somatic symptoms can be present with other medical and psychiatric diagnoses. DSM-5 recognizes Somatic Symptom and Related Disorders as Somatic Symptom Disorder, Conversion Disorder, Illness Anxiety Disorder, Factitious Disorder, and Psychological Factors affecting another medical condition. Somatization that does not fit into these categories is classified as "other specified and unspecified somatic symptom and related disorders."

Epidemiology

Among patients who present to the primary care setting with physical complaints almost 25% of them have no objective evidence of a physical disease process [2]. Additionally, many patients display and perceive symptoms that can be judged to be out of proportion to the degree of illness present, or perceive symptoms that cannot be explained. Frequently, their attention to these symptoms may be excessive or even disabling.

Etiology of Somatization

Somatization disorders should be conceptualized in the setting of the biopsychosocial model which includes biological factors, psychological factors, and social factors.

Biological Factors

Unfortunately, not much is understood about the biology of somatic symptom and related disorders. Many patients with somatic symptoms often have comorbid anxiety and depressive disorders and utilize the health care system at a higher rate than those without a psychiatric diagnosis [2]. It is known that stress causes changes in the function of the hypothalamic- pituitary axis, but more studies are needed to understand the pathophysiology behind stress and somatic symptom disorders [3].

Environmental and Social Factors

Somatization can be affected by early childhood experiences, cultural beliefs, and psychological factors. Adverse childhood experiences have a significant impact on patients' personality and lifelong health outcomes with about 61% of adults reporting that they experienced at least one adverse childhood experience [4]. Adverse childhood experiences include violence, abuse, neglect, witnessing violence in the home, and growing up in a household with mental health or substance abuse problems. Alternatively, it has been hypothesized that some families have learned to communicate their needs to one another through the language of illness and suffering.

Approach to the Patient

The nature of uncertainty in somatic-related disorders brings anxiety to both the family physician and patient [5]. This anxiety can lead to difficult encounters in which both the patient and family physician experience frustration. It is important for the family physician to be mindful of their bias and perceptions of this disorder which could affect their behaviors toward the patient. The patient struggling with a somatic-related disorder is not feigning illness and there is generally no gain or incentive [5]. In patients with somatic symptom disorder, the patient's suffering is real. It has been noted that even in patients suffering from illness with a clear organic pathology, the experience of suffering is poorly correlated with the extent of tissue damage or degree of functional impairment [6].

There is a group of patients who present with prominent anxiety. They often display an increased focus on bodily signals which leads to

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misinterpretation of harmless signals as alarming and leads to increasing anxiety. Others present as sad and apathetic which can complicate the differentiation between major depression and sadness due to the impact of somatic symptoms. When patients present as passive, they often feel no control over their life and experience a sense of helplessness. Finally, patients may also present as distressed or puzzling to the family physician [7].

The family physician can offer to help the patient to develop the skills to cope with the symptoms and not focus simply on looking for a "cure." Coping will help patients to improve their functioning and quality of life. Patients will also benefit from receiving an explanation that is compatible with the concepts they hold about their own health. In other words, how does the patient think about their health? What do they think is going on? Is there something that makes it better? Empowering the patient to think about and articulate the answers to these questions may increase the patient's level of perceived control over their condition.

Diagnosis

Patients with somatic symptom disorders will usually present to their primary care physician rather than to a mental health professional. This may make the diagnosis of somatic symptom disorder even more difficult, since the default paradigm of the medical system tends to be based on the "ruling out" of various "serious" pathological conditions, rather than actively detecting and diagnosing somatic symptom disorders. Ideally, the diagnosis is made early and is based on the presence of positive symptoms and signs rather than the absence of medical explanations for somatic symptoms. The history of this condition is characterized by the presence of positive symptoms and signs for at least 6 months. Positive symptoms of somatic symptom and related disorders are disproportionate and excessive thoughts about the seriousness of symptoms, persistently high levels of anxiety about health or symptoms, and excessive time and energy devoted to the symptoms or health concerns [2].

Labs and imaging should be limited to only what is medically necessary to prevent unnecessary harm. Increased diagnostic testing can lead to increased false-positive results which can then lead to unnecessary procedures. There is some evidence that increased testing may have complex effects on patient experiences and may lead to increased patient anxiety [8].

Differential Diagnosis

Somatic symptom and related disorders are often comorbid with other psychiatric diagnoses as described above. This can make the differential diagnoses broad. In order to narrow down the differential, it is helpful to determine if the physical symptoms seem to have a psychiatric etiology by considering the following:

To what extent are the signs and symptoms intentionally produced?
Do the symptoms follow traumatic or stressful life events?
To what extent are the symptoms related to a psychiatric diagnosis such as anxiety or depression?
Is there a secondary gain?

Treatment

The management of somatic symptom disorder can be frustrating for the family physician. While these patients are often viewed as challenging, by cultivating the relationship those challenges can be mitigated. When symptoms are seen as medically unexplained, relationship-building strategies are a key tool in the family physician's toolbox. The management of somatic symptom disorders requires a multifaceted approach tailored to the individual patient. To choose the correct treatment plan, primary care clinicians should keep in mind psychological, social, and cultural factors that influence somatic symptoms.

It is recommended that the family physician implement the following strategies: schedule

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regular appointments, establish a strong therapeutic alliance, acknowledge, and legitimize the patient's symptoms, and limit diagnostic testing or referrals to specialists [9, 10] (Table 1).

Recommendations need to be used in a flexible manner as patients may have different presentations of their symptoms.

Physicians who explicitly display sensitivity to the intensity of patients' suffering facilitate the resolution of mild Medically Unexplained Symptoms (MUS). A person who is predisposed to worry in general not only about health concerns may be labeled a "somatizer" if the clinician minimizes or fails to recognize and nonverbal cues to the emotions regarding the patient's worry [11]. If the clinician does not acknowledge the patient's concerns, it can lead to an increase in patient anxiety when they feel they are not being heard. It is imperative to develop awareness of one's reactions to patients, as physicians who feel discouraged and frustrated will struggle to express genuine empathy for the patient's distress and stay present in the relationship.

As demonstrated in the previous section, the approach to the patient is vital to the treatment in primary care. When assisting patients to cope and manage their distress, utilizing non-judgmental and empathetic statements is at the forefront. Communication is a key technique that must be learned for challenging encounters, particularly when there are medically unexplained symptoms. Once the patient perceives the physician is not "on their side," management will be impacted. Some examples of wording that can be used are seen in Table 2.

Education about the symptoms and treatment, commitment to working to help the patient find a way to manage their distress, identifying goals, and negotiation of treatment goals are the main components of the process in the visits. These are techniques that are part of the treatment process. In randomized studies, treatment groups showed clear improvements in physical disability, overall mental health, and decreased use of narcotics and benzodiazepines when these components were incorporated into the visits, compared with controls [5].

Psychotherapy

Psychotherapy is an established treatment modality in patients with somatic symptoms and related disorders, but it has limitations. Various forms of psychotherapy have been recommended for a somatoform disorder such as cognitive behavioral therapy and mindfulness-based therapy. Patients who are considered for referral should be assessed for suitability for psychotherapy [12]. Further,

Table 1 Approach to the patient with somatic symptom and related disorders

Recommendations for patient approach	Purpose and goal
Schedule regular appointments	Regulates the visits to the Emergency Department and excessive calls as well as avoiding the need to have symptoms to get an appointment
Establish a strong therapeutic alliance	Listen to the patient and have empathy for their suffering
Acknowledging and legitimizing patient's symptoms	Validate their experience and verbalize that what they are feeling is real while educating them about the mind and body connection
Limit diagnostics	Limit diagnostics that can be further damaging to a patient's health
Referral to specialist	When referring ensure that there is a specific question that needs to be answered versus a general referral

Table 2 Speaking to patients with medically unexplained symptoms

"Although it is not completely understood there are some interventions we can try that can help you deal with the symptoms better"	"I can see how frustrating not having an answer is for you"
"You are worried that there is something serious going on with your health"	"What are you most worried about"

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some patients with these concerns may never follow through with seeing a therapist because they do not agree that their distress is primarily generated by psychological factors.

Cognitive Behavioral Therapy

Cognitive behavior therapy (CBT) has been found to be an effective treatment of somatoform disorders [12, 13]. It focuses on cognitive distortions, unrealistic beliefs, worry, and behaviors that reinforce health anxiety and somatic symptoms. Maladaptive behavioral patterns (avoidance behavior) along with the socio-occupational and interpersonal impairments are also addressed [12, 13]. Benefits of cognitive behavior therapy include reduced frequency and intensity of symptoms and cost of care and improved patient functioning [12, 13].

Mindfulness-Based Therapy

Mindfulness-based therapy (MBT) has been used effectively to treat a variety of physical and psychological disorders, including depression, anxiety; as well as treating somatization disorders, including fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome.

Mindfulness-based therapies are superior to waitlisted controls in reducing pain, depression, anxiety, symptom severity, and improving quality of life [14].

A memory aid for the approach to and treatment of patients with somatic issues has been proposed. The CARE MD (Consultation/cognitive behavior therapy, Assessment, Regular visits, Empathy, Medical/psychiatric interface, Do no harm) mnemonic was developed to help primary care clinicians recall the elements of working effectively with patients who have somatic symptom disorder [15] (Table 3).

Pharmacotherapy

SSRIs or tricyclic antidepressants have been shown to be effective in alleviating symptoms in patients with somatic symptoms [9, 16].

In a meta-analysis of 94 trials, antidepressants provided substantial benefit. Amitriptyline was the most studied tricyclic and provided benefits for at least one of the following outcomes: pain, morning stiffness, global improvement, sleep, fatigue, tender point score (based on the number and severity of tender points), and functional symptoms [17].

Antidepressants can be initiated to treat psychiatric comorbidities, such as anxiety and depression, which may help in managing the overall emotional distress the person experiences. It does not, however, directly treat the distorted thinking process that is often underlying in persons with this disorder. For this reason, it is important to include psychotherapeutic interventions in the treatment of patients.

Table 3 CARE MD primary care approach

Step	Description
Consultation	Consult and/or collaborate with mental health
Assessment	Evaluate for other medical and psychiatric disorders
Regular visits	Schedule short/frequent follow-up to reduce overuse of medical care (e.g., inappropriate emergency department visits, excessive calls) and avoid the need for the generation of symptoms to get an appointment; stress coping rather than cure
Empathy	Spend most of the time listening to the patient and acknowledge that what he or she is feeling is real
Medical-psychiatric relationship	Emphasize the mind-body connection; avoid comments such as "there is nothing medically wrong with you"
Do no harm	Limit diagnostic testing and referrals to subspecialists; reassure the patient that serious medical diseases have been ruled out

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Cultural Considerations to Treatment Planning

While there are a vast array of cultural worldviews that influence a patient's response to health and illness, some important considerations include the ways in which the patient perceives or defines the problem, how it is expressed (somatically, behaviorally, or affectively) who should be consulted for the condition that is encountered (e.g., medical workers, lay or religious healers, support networks), as the patient or communities' own preferred treatment options.

Variables such as age, gender, race, education, ethnicity, socioeconomic status, language, sexual orientation, religion/spiritual beliefs, geographic location, and physical abilities all influence a person's culture and identity. Help-seeking behaviors may be impacted by these variables and also influence the ways in which distress is expressed by individuals. In many groups, physical symptoms may be perceived to be more acceptable than expressions of psychological or emotional distress. Therefore the expression of emotional discomfort as a somatic symptom – or the "idiom of distress" by a particular patient may be immediately clear to someone familiar with the patient's background and worldview, while another physician may have more difficulty recognizing the patient's physical symptoms as possible manifestations of psychological distress. Recognizing somatic symptoms in context, appropriately addressing symptoms that may represent serious illness, and retaining open lines of communication and trust with patients suffering from somatic symptom disorder coming from different backgrounds and conditions are the most challenging tasks faced by family physicians in everyday practice. A sound understanding of the underlying dynamics and approaches to these conditions will reduce the complexity and uncertainty that often accompany these conditions.

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Selected Behavioral and Psychiatric Problems

35

Amy Crawford-Faucher and Daniel Deaton

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General Principles

Definition/Background

The diverse psychiatric disorders discussed in this chapter are unified by the fact that patients will generally not present to their family physician self-reporting their disorder, as many lack insight into the cause of their symptoms. With eating disorders, the family physician may be tipped off to the diagnosis by concerned family members or by physical signs and symptoms of the condition. Patients with personality disorders may elicit strong reactions from the physician and staff and may behave in ways that seem to contradict the achievement of good health. Within each group of disorders, there are specific diagnostic criteria described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [1, 2]. In either case, the specific psychiatric diagnosis may not be as important as is gaining general insights into the psychopathology and developing strategies to engage the patient as an active participant in their care.

Eating Disorders

Eating disorders encompass a range of abnormal thoughts and behaviors surrounding food, eating, and weight control. In anorexia nervosa and bulimia nervosa, distorted body image and sometimes an extreme fear of body fat are at the core of the condition. Binge-eating disorder is associated with shame, obesity, and increased risk of metabolic syndrome. Pica, rumination disorder, and avoidant/restrictive food intake disorder are not associated with disturbed self-image but may cause significant medical complications. The prevalence of any eating disorder in the general population varies throughout the world but is thought to be about 1%. They appear to be more prevalent in high-income, developed countries, but there are insufficient epidemiological studies from low- and middle-income countries [3]. There can be significant overlap among symptoms of eating disorders, and in some cases, patients do not meet criteria for a single diagnosis.

Diagnosing an eating disorder can be challenging. Patients who seek help on their own often complain of the physical sequelae of low body weight and malnutrition, such as fatigue and constipation, or the psychological symptoms associated with starvation such as depression and anxiety. For the family physician, recognizing aberrant behaviors and thoughts and treating resulting medical complications holistically can assist the patient to get the comprehensive care that is needed for effective treatment.

Anorexia Nervosa

Anorexia nervosa (AN) is a disease that most commonly manifests in adolescence or early adulthood. While it has been traditionally associated with girls and young women in high-pressure, high-achieving families and societies, it is important to recognize that all ethnicities, children, boys, and older women and men can also be affected. The hallmarks of AN are persistent and inadequate energy intake to provide metabolic needs, intense fear of gaining weight or becoming fat, and disturbed self-perception of weight and shape. The DSM-5 recognizes subtypes including restrictive, where weight loss is achieved through dieting, fasting, and/or excessive exercise, and a binge-eating/purging type, where the person

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abuses laxatives, diuretics, or enemas to counteract any weight gain from binge-eating. It is also important to understand that variations exist: women with type 1 diabetes are at increased risk for eating disorders and may withhold insulin to achieve weight loss [4], and there are case reports of patients who develop anorexia after gastric bypass surgery [5]. The lifetime prevalence of anorexia is 0.5% in US women. Some cultural groups, including Latino and African Americans, may express less "fat phobia." Asians may relate their decreased food intake to gastrointestinal disturbances. Anorexia is 10 times more common in females than males [6], and the age of onset is typically late adolescence.

Diagnosis

The DSM-5 has amended the requirements for diagnosing anorexia nervosa. It removed the requirement for amenorrhea and the need to be less than 85% of expected weight. The new weight loss definition requires weight below a minimally normal level for age, sex, developmental trajectory (for children and adolescents), and physical health. The Centers for Disease Control and Prevention (CDC) and World Health Organization use body mass index (BMI) less than 18.5 kg/m^2 to define low body weight in adults, and WHO uses BMI less than 17 kg/m^2 for "moderate or severe thinness." Using a BMI-for-age percentage can be helpful for children and adolescents, with BMI-for-age less than the fifth percentile to suggest underweight. The DSM-5 cautions, however, that children above that cutoff can be affected by low weight if their growth is impaired.

Patients with anorexia rarely complain of weight loss. A hallmark of the disorder is distorted self-view and continued belief in either general obesity or fat target areas on the body. Extreme malnutrition causes physiological symptoms which may be distressing enough to bring the patient to medical attention, including amenorrhea, fatigue, constipation, early satiety or bloating, palpitations, fainting, and sometimes depression or anxiety. Starvation also impairs cognitive function which further impairs insight into the disorder.

On physical exam, in addition to significant emaciation, patients may show significant abnormalities in vital signs, including hypothermia, hypotension, and bradycardia. Skin may be dry, with thinning hair and sometimes lanugo. Peripheral edema may be present when the patient stops laxative or diuretic abuse or starts to regain weight. Laboratory abnormalities are also due to chronic starvation (see Table 1).

Behavioral changes may be reported by family members, as the patient may either lack insight or feel secretive about eating and or purging activities. The degree of functional impairment varies, as some are able to continue school, professional, and social activities. More severe cases may be significantly less able to function. The differential diagnosis includes other disordered eating patterns associated with major depression, substance abuse, or schizophrenia such as avoidant/restrictive eating, but these conditions are distinguished from anorexia by the lack of fear of gaining weight. Medical conditions predisposing to poor oral intake include gastrointestinal disorders, occult malignancies, or HIV disease.

Treatment

The type and intensity of treatment for anorexia depends on the severity of weight loss and medical complications. Those with extremely low weight, comorbid medical conditions, or significant laboratory and physical abnormalities need to be hospitalized for close monitoring as refeeding is started. The medical goals of treatment include replacing electrolytes and monitoring the refeeding process. Refeeding syndrome is a serious complication which can lead to significant fluid and electrolyte shifts that can predispose to heart failure and sudden cardiac death. Preventing refeeding syndrome requires a structured refeeding plan with careful increases in calories and protein as well as monitoring of electrolytes. Comprehensive eating disorder centers use a variety of protocols, but many include nasogastric

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Table 1 Physical and laboratory abnormalities in anorexia nervosa

Physical signs	Notes
Marked weight loss	Weigh patient in hospital gown; do not allow her/him to look at scale
Hypothermia	Temp <96% F may indicate need for admission
Hypotension, orthostasis	SBP < 90, positive orthostasis, consider admission
Sinus bradycardia	<50 BPM day, <45 BPM night, consider admission
Murmur	Mitral valve prolapse can develop with starvation
Dry, brittle hair and nails	Chronic malnutrition
Lanugo	Chronic starvation and hypothermia
Peripheral edema	Heart muscle wasting, response to refeeding
Abdominal bloating	Can occur with any refeeding
Lab and ECG abnormalities	
Sinus bradycardia, prolonged QTc	Combination predisposes to ventricular arrhythmias and sudden cardiac death
↓ glucose, potassium, calcium, magnesium, phosphorous	Particularly dangerous in the setting of prolonged QTc
↑ blood urea nitrogen (BUN), creatinine	Dehydration, prolonged activation of renin-angiotensin-aldosterone system
↑ alanine aminotransferase (ALT), aspartate aminotransferase (AST)	Steatosis from prolonged or severe starvation
↓ triiodothyronine (T3), ↑thyroxine (T4)/T3 ratio Normal TSH	Starvation-induced euthyroid sick syndrome; self-corrects with weight gain

References [7, 8]

feeding until the patient is willing and able to eat sufficiently.

Psychiatric treatment for anorexia includes comprehensive refeeding, as the starved brain may lack the ability to develop insight about dysfunctional weight perceptions. Psychotherapeutic treatment of anorexia is crucial. The Maudsley method is a family-based therapy that is effective in teens with anorexia, especially within the first 3 years of illness. Individual cognitive behavioral therapy (CBT) and group therapies are also widely used. Selective serotonin reuptake inhibitors can be used to treat comorbid depression and anxiety, but have not been shown to improve weight gain or prevent remission [7, 9].

Prognosis

Most patients with anorexia nervosa experience full or partial resolution of their condition within 5 years of diagnosis, but up to 20% may experience chronicity [10]. The crude mortality rate is 5% per decade and often due to medical complications or suicide [1].

Bulimia Nervosa

Similar to anorexia, those with bulimia nervosa (BN) have negative feelings about their bodies and a distorted relationship with food. Unlike anorexia, patients with bulimia tend to be normal to overweight and consequently may not come to medical attention as dramatically. The hallmarks of the disorder include binge-eating with compensatory purging behaviors to avoid weight gain. Bulimia primarily affects young women and is more common than anorexia, with a prevalence in the United States of 2–3%. It occurs with similar frequency in many other high-income countries. The underlying risk factors are similar to

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anorexia, but there is a higher burden of comorbidity with anxiety, depression, and borderline personality disorder [1, 6, 7].

Diagnosis

The DSM-V defines binge-eating as episodes of unnaturally large food intake that is accompanied by a feeling of loss of control about eating. This must occur at least weekly over 3 months to meet criteria. Purging through induced vomiting; inappropriate use of diuretics, emetics, or laxatives or excessive exercise are also key to the diagnosis. Binging and purging behaviors may vary over time; some patients may continue to binge without subsequent purging, leading to crossover to binge-eating disorder. While some with anorexia exhibit binge-purge behavior, the diagnoses can be easily distinguished as anorexia requires the patient to have a low BMI.

Medical complications can include menstrual irregularities or amenorrhea. Diuretic or laxative abuse can lead to significant electrolyte disturbances, especially hypokalemia, and consistent laxative abuse can lead to dependence on them for bowel movements. Tooth enamel erosion from repeated exposure to gastric acid is sometimes visible on the lingual surface of the teeth. Rare complications include esophageal tears, gastric rupture, and cardiac arrhythmias. Patients are often ashamed of the binging and purging and may try to hide their behaviors. In between binging episodes, patients may restrict or "diet" to avoid further weight gain.

Treatment

The severity of electrolyte or GI abnormalities dictates the intensity of medical treatment. Patients with severe electrolyte disturbances require hospitalization for electrolyte monitoring and repletion, although they generally correct rapidly once purging has stopped. Treatment of laxative-induced constipation is managed with a combination of reassurance that bowel function will return and judicious use of an osmotic laxative (see Table 2). Cognitive behavioral therapy is the mainstay for treating bulimia. Adjunctive medication, especially high-dose fluoxetine (60 mg daily), seems to be effective in reducing binge-eating and purging. If fluoxetine is not successful, it is reasonable to try other SSRIs as second line pharmacotherapy [11].

Table 2 Abnormalities in bulimia nervosa

Physical exam signs	Notes
Normal or overweight, with fluctuations	From binging and purging
Dental enamel erosion, gum disease	Recurrent vomiting
Parotid gland enlargement	Recurrent vomiting
Calluses on knuckles, hands	Damage from teeth from recurrent self-induced vomiting
Edema	From activation of renin-angiotensin-aldosterone system from chronic laxative or diuretic abuse
Lab abnormalities	
↓ potassium, chloride, magnesium, metabolic alkalosis	From recurrent vomiting or laxative or diuretic abuse
↑ BUN, creatinine, ↑ creatine kinase (CPK)	Prolonged hypokalemia and reduced kidney perfusion from chronic hypovolemia

References from [7, 8]

Prognosis

The remission rate is 80% for bulimia, but an increased crude mortality rate of 2% per decade persists. Death is often due to suicide or, rarely, from medical complications.

Binge-Eating Disorder

Binge-eating is characterized by the same secretive, uncontrolled eating seen in bulimia, but without the accompanying purging. Those with binge-eating disorder report either a specific or generalized lack of control over what they eat that results in large amounts of food consumed quickly in the absence of physical hunger. As

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opposed to bulimia, where dieting often precedes binging, binge-eaters will diet after a binge. Binge-eating often results in overweight or obesity and leads to greater physical and psychosocial impairment than BMI-matched controls. Binge-eating disorder occurs in 0.8% of men and 1.6% of women in the general US population, although the prevalence is much higher among those seeking weight loss treatment. Therapies adapted from bulimia treatment include modified cognitive behavioral therapy and dialectical behavioral therapy. Additionally, some selective serotonin reuptake inhibitors may be beneficial, and topiramate (although limited by side effects) seems an effective addition to CBT for decreasing binge-eating and weight [11, 12].

Personality Disorders

Patients with personality disorders have habitual thoughts, emotions, and patterns of behaving that are maladaptive and result in impaired social functioning. These traits may be present from childhood, though they solidify in adolescence or early adulthood and tend to be stable throughout life. Personality disorders often coexist with other psychiatric and substance abuse disorders, complicating treatment of both. Personality disorders are common, with a community prevalence of 4–13% for any personality disorder, but are even more prevalent in medical settings, with estimates that 30–45% of psychiatric outpatients and about 24% of primary care patients could meet criteria for any personality disorder [13–15].

There are 10 distinct personality disorders described in the DSM-V, but a significant proportion of patients may exhibit traits of more than one disorder. As patients often lack insight into the source of their continued crises or instability, appropriate diagnosis can require repeated evaluations over time and input from others close to the patient. Given the potential for continuity and long-term doctor-patient relationships, family physicians may well see these patients more than any other specialty, including psychiatry. As patients with personality disorders can be challenging, it is important to develop strategies to recognize personality disorders and traits in order to provide the best care and minimize physician and staff frustration and burnout.

While personality disorders tend to be set from early adulthood, patients may generally function well and not come to clinical attention until later in life, often when support systems are lost. Personality disorders are distinguished from other psychiatric disorders by the fact that the fixed thought and behavior patterns occur persistently and not only in the context of a psychotic or mood disorder. Conversely, it is important to recognize that while patients may have personality traits that may be suggestive of a disorder, the threshold for diagnosis may not be reached unless those maladaptive responses cause impairment or distress.

Research is ongoing about other models of conceptualizing and categorizing personality disorders, but the DSM-V maintained its previous organizational structure for personality disorders, categorizing the disorders into clusters: A (paranoid, schizoid, schizotypal), B (antisocial, borderline, histrionic, narcissistic), and C (avoidant, dependent, obsessive-compulsive) [2].

There is growing evidence that despite the traditional view of the fixed nature of these disorders, some patients may improve symptomatically over time. The fundamental treatment for personality disorders is therapy. Cognitive behavioral therapy (CBT) and dialectical behavioral therapy (DBT) are commonly employed. CBT uses cognitive restructuring, skills training, and behavior modification to help improve functioning. DBT is a form of CBT that is widely used in borderline personality disorder and in others with suicidality and incorporates individual and group therapy. It recognizes the patient's underlying extreme reactions to events and helps the patient accept the underlying predisposition and learn skills to help overcome destructive thoughts and behaviors. Treatment of some personality disorders, such as borderline personality disorder, has been studied more thoroughly than others. There are no FDA-approved medications for treating personality disorders, but there is some evidence for

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off-label use for specific associated symptoms such as impulsivity, aggression, or anxiety [16].

Cluster A Personality Disorders

Patients with cluster A personality disorders often appear eccentric and odd. As children and adolescents, they may have been loners who had poor peer relationships and may have been teased for exhibiting odd behaviors and not following social norms. Those with cluster A disorders may be less likely than the general public to establish primary care, as they are essentially mistrustful.

Paranoid Personality Disorder

Patients with paranoid personality disorder have a basic and pervasive mistrust of others that is characterized by suspicions of exploitation and doubts of trustworthiness and fidelity in friends, family members, and coworkers. These characteristics can make patients difficult to get along with and make close relationships difficult. Their response to perceived threats can make them litigious and also prone to fanatical worldviews. Prevalence in the general population is likely between 2% and 4% but may be lower in primary care populations as these patients may not seek care. Some case reports indicate improvement in functioning with CBT [17].

Schizoid Personality Disorder

Those with schizoid personality disorder often appear aloof and impervious to the needs of human interaction. They almost always choose solitary hobbies and jobs and may not have any close relationships beyond first-degree relatives. National surveys suggest a prevalence of 3–5% of the general public but it is uncommon in clinical settings; patients may not see their personality traits as distressing and consequently do not seek treatment. Schizoid personality disorder is more common in families with schizophrenia, suggesting the possibility of a genetic influence.

Schizotypal Personality Disorder

Patients with schizotypal personality disorder come across as odd. They share the fundamental discomfort with intimacy with schizoid personality disorder but in addition may be eccentric and have distorted thoughts – "magical thinking" – that influences behavior and is outside of the cultural norm. They tend to be anxious in social situations and may have few close relationships. Patients with schizotypal personality disorder may seek treatment for anxiety or depression rather than for the disorder itself. The reported prevalence of about 4% is higher in the general public than it is in psychiatric or primary care settings (up to 2%). There is some evidence that low-dose atypical antipsychotic medications can improve executive function and reduce negative symptoms [16].

Cluster B

Cluster B disorders are characterized by manipulative and impulsive behavior, although the motivations for these behaviors is different; those with antisocial personality disorder manipulate others for power or acquisition, while those with borderline personality disorder will manipulate for attention and nurturing.

Antisocial Personality Disorder

Antisocial personality disorder (or psychopathy) is characterized by a pervasive disregard for the rights of others and is manifested by repeated illegal behavior, deceitfulness, impulsivity, aggressiveness, consistent irresponsibility, and lack of remorse. While the diagnosis cannot be made until age 18, evidence of conduct disorder starting by age 15 is part of the criteria. While the overall prevalence of this disorder is low – 0.6–

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3% – not surprisingly, the rate is much higher among those in the criminal justice system, where just under 50% of prisoners worldwide meet criteria [18]. The condition is also commonly associated with other psychiatric conditions and can complicate the treatment of the same. Evidence-based pharmacologic research is limited to therapies for impulsive aggression that suggest benefit from lithium and phenytoin [16].

Borderline Personality Disorder

Borderline personality disorder appears to be relatively uncommon in the general population – about 2% – but comprise 6% of primary care visits, 10% of those in outpatient mental health clinics and 20% of inpatient psychiatric patients [19]. The fundamental criteria of this disorder include pervasive instability of interpersonal relationships and self-image, resulting in significant impulsivity, including suicidality and self-mutilation . Those with borderline personality disorder constantly guard against real or imagined abandonment, and this fear drives intense and unstable relationships and a sense of constant crisis. Patients with borderline personality disorder may initially idealize certain providers or partners, only to suddenly "flip" or "split" and devalue them when the perceived support is not sufficient. This "splitting" is frequently the first concrete sign of this personality disorder noted by providers. There is significant overlap with other psychiatric disorders, including mood disorders, eating disorders (especially bulimia), and substance abuse.

Borderline personality disorder is the most studied personality disorder, with extensive evidence about therapy and psychopharmacologic treatments. CBT and DBT can be effective; evidence-based guidelines recommend selective serotonin reuptake inhibitors for impulsive aggression and have found some benefit from aripiprazole, mood stabilizers, and anticonvulsants, especially topiramate, on multiple symptoms. However, studies show minimal effect on overall disease severity and many of these medications require monitoring and they can have significant side effects [20].

Histrionic Personality Disorder

Histrionic personality disorder manifests by patients who are excessively emotional and attention-seeking. They will use speech, dress, or sexual provocativeness or other means to maintain the center of attention. This resulting drama can impair job and relationships as they are needy for but cannot truly achieve intimacy. The prevalence is <2% in the general population, but may be higher in primary care settings because of heightened medical concerns.

Narcissistic Personality Disorder

Narcissistic personality disorder is also uncommon – 0.8% up to 6% depending on the criteria used, but may be over represented in clinical populations. People with this disorder can be grandiose, with a sense of entitlement, belief that they are special and should only associate with other special or high-level people, and may lack empathy and be extremely sensitive to any criticism or defeat.

Cluster C

Cluster C personality disorders are all characterized by anxiety that is manifested in different ways. The avoidant, dependent, and obsessive-compulsive personality disorders may coexist with mood disorders which may drive patients to seek medical attention for anxiety, depression, or somatic complaints.

Avoidant Personality Disorder

Those with avoidant personality disorder have an inordinate fear of criticism, disapproval, or rejection that manifests as social inhibition and feelings of inadequacy. They can appear as very shy, quiet, and timid and may avoid new social or job-related experiences because of fear of ridicule. The reported prevalence is about 2% in the general public. Treatment is not well studied, but

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small studies show improved functioning with both group and individual CBT [17].

Dependent Personality Disorder

Dependent personality disorder is characterized by a pervasive need to be cared for, paired with an inordinate fear of separation. Patients with this disorder have difficulty functioning independently, which can lead to problems at work and lead to submissive behaviors in relationships, including an unwillingness or inability to leave abusive relationships. In the primary care office, these patients may take a lot of time to feel cared for or seem unable to follow through with self-care recommendations. This disorder is uncommon, estimated at about 0.5% in the general population.

Obsessive-Compulsive Personality Disorder

Those with obsessive-compulsive personality disorder are motivated by a pervasive need for control, which is manifested by preoccupation with order, perfectionism, and inflexibility. The self-imposed high standards can cause significant anxiety and dysfunction. This disorder is distinguished from obsessive-compulsive disorder (OCD) because it lacks the presence of compulsive behaviors. These patients may live below their economic means and may be prone to hoarding. The prevalence is thought to be between 2% and 8% of the general population, making it one of the most common of the personality disorders. Multiple psychotherapeutic treatments have shown benefit, and SSRIs may be effective in treating accompanying anxiety.

Table 3 Strategies for effective engagement and management of patients with personality disorders in primary care

Cluster traits	Manifestations in primary care encounter	Strategies
Cluster A traits		
Mistrust of others	Expect critical comments, litigious threats	Allow patients to vent frustrations without confirming or confronting paranoid beliefs
Difficult to engage in therapeutic relationship	May discount recommendations	Provide consistent, professional attitude without becoming too informal
Odd thoughts and behaviors	May have unusual health beliefs	Expect and tolerate eccentric beliefs and behaviors
Excessive social anxiety	May not get more comfortable with physician relationship over time	Provide clear explanations without becoming overly friendly, warm, or humorous
Cluster B traits		
Manipulative	May be drug-seeking or have frequent disability claims	Be empathetic, but set clear limits despite angry outbursts from patients; recognize the physician's need to "do something" in response to demands
Heightened emotional responses	Suicidal threats, gestures	Set safety goals and communicate to other team members
Somatization	Frequent office visits or calls for medical concerns	May do well with regularly scheduled and somewhat frequent follow-up to minimize emergency calls and crises
Cluster C traits		
Hypersensitive to criticism, shame, or rejection	May seem evasive with direct questions	Validate patient's concerns and encourage patient to report symptoms
Fear of losing control	May perseverate on details and miss big picture	Provide thorough and detailed evaluations, but do not highlight uncertainties in treatment or prognosis
Fear of separation	May be in abusive relationships	Provide reassurance, frequent scheduled follow-up

References [21–23]

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Management in the Family Medicine Practice

As patients may exhibit traits from multiple personality disorders, lack insight into the source of their distress, and not be willing to accept a diagnosis, managing patients with personality disorders can be challenging. It may take a long and trusting doctor-patient bond for a patient to accept a referral to behavioral health. In the meantime, there are strategies the family physician can use when working with personality-disordered patients (see Table 3).

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Anxiety and Stress in Young Adults

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Laeth S. Nasir and Amy E. Lacroix

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General Principles and Background

Small amounts of stress (emotional strain) are beneficial and healthy and help individuals to perform better, whether at work, in relationships, or in physical activities. Excess stress can lead to both mental and physical illness. Individuals perceive stress differently: the same demands asked of one person may cause great stress and in another hardly any. As young adults make their way through new experiences in work and relationships, they experience stress and have to learn how to navigate through it effectively. Some persons who experience high levels of stress will go on to develop persistent anxiety symptoms. Other individuals may have anxiety that does not seem related to external stressors. Sometimes a prominent familial component is present. It is often unclear whether this is a genetic predisposition or learned behavior.

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Anxiety can be defined as chronic and persistent worry, which is multifocal, excessive, and difficult to control [1]. Anxiety disorders (AD) are the most common psychiatric disorder of adults, affecting as many as 30% of adolescents and adults at some point in their life [2]. They are the sixth leading cause of disability in both high- and low-income countries with the highest rates between ages 15 and 34 [3]. Anxiety disorders often have their onset in childhood and adolescence. Some anxiety disorders are more common in childhood (e.g., separation anxiety) than adulthood (e.g., generalized anxiety disorder). Developmentally, as demands to perform increase, whether in school, work, or relationships, more opportunities arise for fears to occur based on prior experiences. It is crucial that the family physician be able to recognize and assist young adult (YA) patients experiencing excessive levels of stress or AD.

Child abuse, physical punishment in childhood, a parental history of mental disorders, low socioeconomic status, and harsh or overprotective parenting styles are all associated with an increased risk of anxiety disorders [4]. In addition, social stressors include experiences of ethnic or racial discrimination, bullying, and social rejection which can result in increased stress and anxiety [5]. Another, more recent phenomenon that appears to be linked to stress and anxiety in YA is exposure to social media [6].

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) classifies anxiety disorders into three types. It separates primary anxiety disorders from obsessive-compulsive disorders and trauma- and stress-related disorders. Several types of primary anxiety disorders exist, including general anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), specific phobias, agoraphobia, separation anxiety, and others. Young adults tend to experience specific phobias, social anxiety, panic disorder, and general anxiety disorder most often. The criteria for GAD based on the DSM-5 are as outlined below:

DSM-5 Criteria for Diagnosis of General Anxiety Disorder

- Excessive anxiety and worry about various events have occurred more days than not for at least 6 months.
- Difficulty controlling the worrying.
- Anxiety and worrying are associated with at least three of the following six symptoms: restlessness or being "on edge," being easily fatigued, difficulty with concentration, irritability, muscle tension, and sleep disturbance.
- The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in important areas of functioning (e.g., work, relationships).
- The disturbance is not due to physiologic effects of a substance or medical condition.
- The disturbance is not better accounted for by another mental disorder.

(Adapted from the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), 2013.)

Epidemiology

According to the National Institute of Mental Health, as many as 32% of adolescents have experienced an anxiety disorder in the last year [2]. Estimates of lifetime prevalence rates of anxiety disorders range from 13 to 33%. According to the World Health Organization, while approximately half of cases of anxiety disorder are recognized, only 1/3 are offered treatment. In one study only 20% of patients with anxiety sought help from health care, and in those who did seek help, about 25% received no treatment at all [7]. Research shows that the annual and lifetime prevalence of AD among females are 1.5–2 times as high as that of males. Patients who are nonheterosexual and gender nonconforming have a higher prevalence of all mental health problems and should be screened regularly [8]. Unemployment and chronic illness are both associated with increased risk for anxiety disorders. A growing body of literature is developing on the effects of social media in creating stress in adolescents and young adults; there is clearly a correlation between mental health problems and media use. A recent systematic review reported that social media use correlated with anxiety, depression, and psychological distress [9]. However on the other hand, social networking may also improve

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social support and interpersonal connectedness, which can decrease stress in YA [10].

Etiology

Persistent or disproportionate anxiety is thought to involve a dysregulation of the normal physiologic response to stressors. It is hypothesized that in disabling anxiety, people experience deficits in the extinction of fear. Human survival depends on an immediate response to a potentially injurious stimulus that leads to self-preservation. In patients with an exaggerated response to stress, minor stressors lead to an overreaction that is inappropriate to the situation and causes dysfunction in a particular situation (as in PD) or in general life functions (as in GAD). Functional MRIs in individuals with anxiety show that the areas of the brain that are most involved include the limbic tract, specifically the amygdala and the insula, as well as their connections to the prefrontal cortex [5].

Genetic predisposition for AD exists, and a good family psychiatric history is essential in all patients with possible AD. Risk in first-degree relatives of patients with an anxiety disorder is estimated to be 4–6 times higher that controls. Specific genes have been associated with PD, SAD, and GAD, but they are clearly complex and multifactorial in nature [11].

Clinical Presentation

Anxiety disorders often present to the clinician with somatic symptoms that patients do not recognize as being stress related. Common symptoms include but are not limited to the following: abdominal pain, headaches, sleep problems, chest pain, chronic back pain, episodes of tachycardia, sweating, chest tightness or difficulty breathing, shaking, and light-headedness or dizziness. Many patients have problems with concentration and present to the physician seeking treatment for attentional disorders. Many patients with AD have already used substances in an attempt to treat their disorder, most commonly alcohol and marijuana, but also sleep aids such as diphenhydramine and melatonin, and sometimes prescription drugs that might include anxiolytics. There is also a strong link between sleep deprivation and anxiety [12].

Not uncommonly patients with AD have comorbid diagnoses that most often include SUD or major depression (MD). It is important to rule out substance use disorders (SUD) when making a diagnosis of an AD in patients. Research has demonstrated that anxiety in adolescents is associated with the development of SUD in later life, and also, patients with AD are more likely to develop a SUD than those without [13].

Panic attacks (PD) are isolated episodes of a constellation of symptoms that may be precipitated by a known/expected event (going to school, public speaking, being in a crowd) or may come on suddenly without warning (see the DSM-5 criteria for PD below). Many who experience them feel as if they might die and are worried that they are having a heart attack or "going crazy." Often persons with panic attacks feel chest pain, dizziness, dread, and profuse sweating. Sometimes they have shaking and paresthesias. Very often, especially with the first attack, they end up in the Emergency Department. Although normal testing can be reassuring in the short term, the medicalization of anxiety may paradoxically result in an escalation of concern and worry.

Patients suffering from comorbid panic disorder and major depression are also at higher risk of self harm [14].

DSM-5 Criteria for Panic Disorder

(A) Recurrent unexpected panic attacks. This includes a surge of intense discomfort that peaks within minutes and includes four or more of the following symptoms: palpitations, sweating, trembling/shaking, shortness of breath, choking, chest pain, nausea or abdominal pain, dizziness, chills or heat sensations, paresthesias, derealization or depersonalization, fear of losing control or going crazy, and fear of dying.

(B) At least one of the attacks has been followed by 1 month of one or both of the following:
   1. Persistent concern or worry about additional attacks or their consequences.
   2. A significant behavior change related to the attacks (designed to avoid precipitating an attack).

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(C) The attack is not related to the effects of a substance or another medical condition.
(D) The disturbance is not better explained by another mental disorder.

(Adapted from the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), 2013.)

Differential Diagnosis

The differential diagnosis of both GAD and PD is important to consider in all patients. A thorough history and physical exam are crucial to eliminate other causes of symptoms: arrhythmias, orthostatic hypotension, thyroid disease, asthma or other pulmonary diseases, and epilepsy should be included in the differential. Screening tests to consider based on a positive history or exam might include thyroid-stimulating hormone or an electrocardiogram. An exhaustive battery of tests is unnecessary and counterproductive in most cases, as it often leaves patients feeling as if the physician has simply "given up" on finding a "real diagnosis." If the physician strongly suspects GAD or PD, it is important to state this directly at the initial visit and let the patient know that other testing is being done simply to solidify the diagnosis.

Table 1 Generalized Anxiety Disorder 7-item scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	>50% days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

GAD-7 Questions from Spitzer et al. [15]

Evaluation for Anxiety Disorders

Evaluation of patients for anxiety disorders should be done in a standardized fashion. The most common simple office based screening tool for evaluation of anxiety in adults is the General Anxiety Disorder-7 (GAD-7) Screen (Table 1). This is a short, seven-question tool that has been well validated for identifying problematic anxiety in adults. It can be used as an initial screening tool in patients suspected of having an anxiety disorder. These tools are simple for patients to fill out, available in multiple languages, and easy to access and evaluate.

Comorbid problems with chronic health, mental health conditions, and SUD are common in patients with AD, both as results of the condition and as precursors. Up to 35% of people with GAD self-medicate with drugs. The clinician needs to screen carefully for substance use disorders, using tools such as the CAGE or CRAFFT questions or with the assistance of behavioral health staff [16].

Treatment Options

The two primary treatment options that have proven most effective for treating anxiety in YA are cognitive behavioral therapy (CBT) and specific medications. Combining the two therapies yields greater efficacy. Mindfulness-based stress reduction (MBSR) therapy is a newer treatment

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modality that shows great response in some patients, especially with general stress management but also in anxiety disorders.

Cognitive Behavioral Therapy

Data on CBT show that its effectiveness is significant, but varies depending on the type of anxiety being treated [17]. Patients who are treated with CBT should be counseled that they will be making an investment in their long-term health that will benefit their mental health for the rest of their life. Usually they are asked to invest 8–12 sessions in learning valuable ways to identify potential stress-inducing situations, modify their thinking about situations, and subsequently work to change reactions that happen in response to stressors. This type of therapy can be done by different specialists in behavioral health (BH), including psychiatrists, psychologists, licensed mental healthcare providers, and some social workers with specific training in CBT. In the past 10 years, more options for CBT delivered electronically have been studied, and some are proving to be equally effective [18]. They are especially useful when working with patients in areas where there is limited access to behavioral health specialists. Many electronic applications ("apps") have been created over the past decade that are designed to assist in management of stress and anxiety, many of them using CBT or mindfulness-based stress reduction (MBSR) (see below).

Medications

Many medications have shown effectiveness in treating anxiety. The most commonly used medication in anxiety treatment are the selective serotonin reuptake inhibitors (SSRIs) and the serotonin and norepinephrine reuptake inhibitors (SNRIs). This group of medications has been well studied and proven effective in treating anxiety disorders in multiple trials with very good results and is the mainstay for treating anxiety. The drawback to using these medications are that they are slow to act. Patients need to be instructed that it will take weeks or even months for medications to become effective. This is quite difficult for someone already experiencing what they consider to be unbearable stress. Medications are usually started at the very lowest end of dosing and increased every 2–4 weeks until (1) symptoms are improved, (2) undesirable side effects are encountered, or (3) the maximum dose is reached, and patient still has no response to the medication.

Medication side effects are common and should be addressed as well. Many of the SSRIs/SNRI' have an effect on libido. This can make them less desirable for YA. Gastrointestinal distress may occur common in the first week or so but usually improves with time. Some persons experience insomnia on the medications and that is why they are usually dosed in the morning. However, other patients may experience drowsiness, so changing the dose to evening might be necessary. It is also essential to ensure that patients have an "emergency plan" in place for severe episodes of anxiety or depression. This should include who they would call or talk to and a backup such as the suicide hotline. Counseling all young adults to keep the suicide hotline number in their cell phone just in case they (or a friend) need it is important. (See Table 2 for the most commonly prescribed medications for anxiety and their dosing recommendations.)

Other Commonly Used Medications for Treatment of Chronic Anxiety

Benzodiazepines show great effectiveness in the treatment of anxiety symptoms, but due to their potential for abuse and dependence, they should rarely be used for anything but short-term treatment. They are considered second- or third-line treatment and should be avoided in patients with a history of alcohol or other SUD. When used appropriately, they can offer relief until long-term control with other medications and therapy is achieved. They are helpful in managing patients with situational anxiety, such as fear with a medical procedure or fear of flying. They are also sedating and have some amnestic properties and should never be used when working or driving.

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Table 2 Medications commonly used in the treatment of anxiety

Medication	Class	Trade name	Starting dose	Maximum daily dose	Side effects/other
Fluoxetine	SSRI	Prozac	10 mg QAM	80 mg	Often activating
Sertraline	SSRI	Zoloft	25 mg QAM	200 mg	Drowsiness, GI distress
Paroxetine	SSRI	Paxil	10 mg QAM	60 mg	Contraindicated in minors
Escitalopram	SSRI	Lexapro	10 mg QAM	20 mg	Sweating
Citalopram	SSRI	Celexa	20 mg QAM	60 mg	Sweating
Duloxetine	SNRI	Cymbalta	30 mg QAM	120 mg	Nausea, dry mouth
Venlafaxine	SNRI	Effexor	37.5 mg QAM	225 mg	Paresthesias
Buspirone	Azapirone	Buspar	10 mg BID	60 mg	Sweating, insomnia
Quetiapine	Antipsychotic	Seroquel	25 mg daily	300 mg	Sedating
Hydroxyzine	Antihistamine	Atarax, Vistaril	25 mg Q6°	100 mg Q6°	Sedating, for acute use

Buspirone is an azapirone anxiolytic and is effective in some patients with GAD.

Beta-blockers such as propranolol are useful in prevention of performance anxiety (such as test-taking, giving speeches, etc.), but are not useful in other types of AD. Tricyclic antidepressants also have been used successfully in treating AD, but their safety profile is less desirable, so are used less often. Anxiety is not considered a primary indication for these drugs. When using them a good cardiac history is essential as they can prolong QT interval and are more lethal if overdosed or taken by a child. Bupropion has not shown strong evidence of effectiveness in treating anxiety. Drugs that stimulate gamma-aminobutyric acid receptors (GABAergic drugs) also have been shown to have some effectiveness in treating anxiety (pregabalin, gabapentin). Prazosin has shown some efficacy in treating post-traumatic stress disorder in patients but is not useful in AD alone. Hydroxyzine is FDA approved for the treatment of anxiety and may be an option if other medications are not good options. None of these drugs have anxiety as a primary indication for their use.

When initiating treatment, the provider should generally start low and advance dosing slowly. Patients with AD are often very sensitive to medications, so should start at a lower dose. The dose can be increased every 2–4 weeks depending on tolerance. However, they are often not effective until a relatively high dose is reached. It is usually recommended that patients continue on medication for a minimum of 6–12 months of positive response before considering discontinuation of the medication. The dose should be tapered gradually over weeks to months. Relapse, unfortunately, can be common, both with treatment with CBT and medications, and may be as high as 40%. Use of alcohol should be discouraged in patients on medication for anxiety, as it may result in dangerous interactions.

Alternative Therapies for Anxiety and Stress in Young Adults

Many other treatments have been evaluated for anxiety. Most recently, MBSR has been shown to have some effectiveness in anxiety treatment and can be recommended as having moderate effectiveness [19]. Mindfulness is defined as the practice of "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" [20]. It is a form of behavioral therapy that has its origins in Buddhism and meditation. It has become the focus of anxiety and stress treatment by many BH specialists. Many web-based apps focus on MBSR and are widely utilized by YA. Their ease of accessibility is attractive to YA patients.

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Endorphins released by exercise might be also helpful in alleviating stress and anxiety in young adults. Exercise has been studied as treatment for anxiety and stress, and early data seem to show that it is a good adjunctive therapy to treating both, though less effective than medications [21]. The clear health benefits of exercise make it a reasonable suggestion for stress relief in many patients if they are willing to invest the time.

Most studies done on other modalities for treatment of anxiety (including yoga, hypnosis, music, pet therapy, reiki, acupuncture, and massage therapy) do not show significant effects or are too small or of too poor quality to yield significant results. However, they do not have any adverse side effects, and many are helpful for overall mobility and fitness. The most commonly used herbal medications to treat anxiety include kava, lavender, and valerian. They are not FDA-regulated products and need to be scrutinized for authenticity and potency. They should be used very cautiously and can cause toxicity if used inappropriately or concomitantly with prescribed medications.

In recent practice, many providers are faced with young adults experiencing AD who are coming forward with requests to have their pets approved as "therapy pets." There is some data that show benefit in overall health and mood from a relationship with a pet. More literature exists about companion animals relieving loneliness than other mental illnesses, but there is some data suggesting that they do improve stress in young adults [22]. When approached about the idea of having a pet as therapy, patients should be reminded that their mental health is their responsibility, and they should be using proven methods to treat themselves. If a pet helps to ameliorate their loneliness and get them some exercise, that may be a benefit. But they should not expect getting a pet to make their anxiety disappear, and in some cases the added responsibility of caring for a pet can add to stress.

Marijuana use has become popular in YA patients as a means of decreasing stress and anxiety. All patients with anxiety should be screened for its use. As it is becoming legalized in many states, we can anticipate its use more often. Good clinical trials are lacking on its effectiveness, and its use by adolescents and YA should be discouraged as it is known to have negative effects on the developing brain [23]. We do not fully know the effects of combining marijuana with other drugs commonly used to treat depression. Cannabidiol (CBD), the nonpsychoactive component of marijuana, has some preliminary studies that suggest that it may be helpful in treating anxiety, but they are limited at this time [24].

Useful Resources for Young Adult Patients

- Anxiety and Depression Association of America: www.adaa.org
- National Institute of Mental Health: https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml
- www.anxiety.org

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Developmental Disability Across the Lifespan

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Clarissa Kripke

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Introduction

The life expectancy of people with developmental disabilities approaches that of the general population. In a healthy, supportive environment with education, social support, and opportunity, all people with developmental disabilities

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can be included in their communities and lead meaningful lives. Developmental disability is not a disease, illness, prognosis, or set of specific cognitive or physical traits. Rather, it is a social construct, defined in the Developmental Disabilities Assistance and Bill of Rights Act of 2000 as a severe, chronic disability that manifests during the developmental period of life, and is expected to continue indefinitely. It results in substantial functional limitations in three or more areas of major life function including self-care, receptive and expressive language, learning, mobility, self-direction, capacity for independent living, and economic self-sufficiency. It is a disability that requires special interdisciplinary services and supports and lifelong, individually planned and coordinated care [1]. Developmental disabilities can result from genetics, injury, or intrauterine, perinatal, or postnatal environmental conditions. Developmental disabilities include diagnoses such as autism, cerebral palsy, epilepsy, traumatic brain injury, and intellectual disability.

Most people with developmental disabilities, even those who share the same diagnosis, have a wide range of strengths and challenges. Individual assessment, treatment, education, and support plans are required. Most individuals with developmental disabilities have complex combinations of developmental, behavioral, medical, and psychiatric conditions. The degree of disability experienced by an individual is dependent on their function as well as on the accommodations in their social and physical environment. For example, a person with an intellectual disability and mobility problem may struggle in a group where technical jargon is used, but participate well if the facilitator makes sure the room is wheelchair accessible and people use plain language. Disability can also evolve over time and can be impacted by treatments and chronic disease. Disability can be reduced by how well risks for secondary conditions are identified and managed, the variety and quality of the opportunities the person is offered, the skills they develop, and how well the person is included, served, and supported by their community.

Role of the Family Physician in Team-Based Care

Family Medicine's holistic view of health is the best approach to maximizing the potential of people with developmental disabilities. Developmental disabilities typically have primary or secondary impact on multiple organ systems and include sensory, movement, cognitive, and physical aspects. Sometimes, medical treatments or procedures can improve outcomes. Other times, focusing on building motor, communication, cognitive, or adaptive skills is a more productive approach. Interventions to educate and support families to include people with developmental disabilities in their community can also improve quality of life and health. Like all patients, people with developmental disabilities need support to make healthy lifestyle choices and need preventive screening and care. Family physicians do not need to be experts in all aspects of care for people with complex disabilities. They can provide routine care and take a lead in coordinating interdisciplinary teams of speech, physical, and occupational therapists, specialists, nurses, dentists, special educators, case coordinators, recreational and vocational therapists, direct support professionals, family and friends who provide treatment, care, and support.

Improving Outcomes with Prenatal Counseling and Care

Genetic Counseling and Testing

With increasing accuracy, prenatal genetic screening and diagnostic testing can identify genetic risks and traits. Diagnostic tests such as amniocentesis and chorionic villus sampling can also expose pregnancies to risks such as pregnancy loss, interventions, discrimination on the basis of the results, maternal anxiety, and false positive or negative results.

Prenatal testing, per se, does not provide women with any information on what it might be like to raise a child with a disability. It provides no information regarding where, in the wide range of

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possible phenotypic outcomes, their child might fall. Genetic tests can't tell parents what services, supports, and resources are available to help them; what a child's strengths will be; what they will contribute to their family or community; or what treatments are available now or will be in the future. When counseling women, it is important to provide accurate and unbiased information on all of these issues so they can make informed choices about their pregnancy. Women may use the information to decide to pursue a termination; ensure they deliver at a hospital with an appropriate level of care; or to prepare themselves to welcome their child into a nurturing environment. However, in many situations, prenatal testing raises more questions than it can answer.

How information is presented to families during prenatal genetic counseling can impact the decisions they make regarding the pregnancy, how well they bond with their child, and how quickly they access services and social support for themselves. Even if their child does not have a disability, it can impact how they support and welcome children with disabilities from other families into their communities [2]. Accurate, balanced, and up-to-date information about common genetic conditions for expectant parents and health care providers is available from Lettercase which is a program of the National Center for Prenatal and Postnatal Resources [3].

Manage Environmental Risks and Health-Related Behaviors

Some developmental disabilities can be prevented by better managing environmental risks and health-related behaviors. Contaminated food and water supplies, infectious diseases, environmental toxins from household products, fires, industrial pollutants, poor nutrition, medications, smoking, alcohol, and drugs, and exposure to domestic or community violence can increase the incidence and prevalence of developmental disabilities. To reduce their patient's risk, family physicians can encourage immunizations, stay abreast of local environmental health issues, take a leadership role in helping their communities adapt to climate change, and participate in public health screenings and interventions which target social determinants of health.

Both younger and older maternal age are associated with increased risks for birth defects. Births to teenage mothers have been decreasing since the 1990s but are still high compared to other industrialized countries. Older maternal age is strongly associated with chromosomal birth defects which can lead to developmental disabilities [4].

Population-Based Developmental Screening for Children

Population-based screening for children for developmental disabilities refers to screening all children who present for primary care as opposed to those who have specific risk factors or when a concern is expressed. The American Academy of Pediatrics recommends conducting developmental surveillance at every health supervision visit and conducting general developmental screening using evidence-based tools at 9, 18, and 30 months. They also recommend autism-specific screening at ages 18 and 24 months [5]. The United States Preventive Services Task Force concluded that there is insufficient evidence to assess the balance of benefits and harms of screening for autism spectrum disorder between ages 18 and 30 months, or for screening for speech or language delay in children aged 5 years or younger [6, 7]. The most common screening tools are parent questionnaires such as the Ages and Stages Questionnaire, Parent's Evaluation of Developmental Status, and the Modified Checklist of Autism in Toddlers (MCHAT) [8].

Assessment

Diagnostic Evaluations

All people who are identified by population based screening; who self-identify as someone with a suspected disability; or whose parents or teachers express concern about development should receive a comprehensive developmental

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assessment in all areas of need. A careful prenatal, birth, and developmental history should be obtained, and if relevant, an educational and vocational history. School records and ancillary information from friends and family can help. Developmental pediatrician or genetics evaluations can be helpful if the etiology of the disability is unclear, a syndrome is suspected, or a genetic diagnosis would change the clinical management. For example, people with Down Syndrome should be monitored for conditions that include hematologic abnormalities, hypothyroidism, hearing loss, cardiac and celiac disease, and atlantoaxial instability [9]. Families may request diagnostic testing to make informed reproductive decisions or to facilitate social connections with other people with similar conditions.

Functional Evaluations

Functional evaluations should include assessments of vision, hearing, and sensory integration, neuromotor function including gait, seizure threshold, and mental health and behavior. Any difficulties with swallow, feeding, skin integrity, continence, and elimination should be assessed. Psychoeducational or neuropsychological testing may be considered. Assessment should also include questions about basic and instrumental activities of daily living. Patients often function much better at home where they may have home modifications or adaptive equipment than they do in the exam room. Alternatively, they may need prescriptions for home modifications or adaptive equipment to improve their function. For example, a patient who use a wheelchair and elevator for mobility in a doctor's office may crawl or use grab bars to walk or climb stairs at home. A person who has difficulty remaining calm in a clinic due to sensory overstimulation may be calm and regulated at home. Home and telehealth visits can provide a fuller picture of a patient's functional strengths and challenges. Observing someone's function in their natural environment may suggest ways in which the environment in their home or community may be improved.

Communication Evaluations

Communication is essential for developing and maintaining relationships, patient care, and self-direction. Everybody communicates. Most people have multiple ways in which they express themselves such as speech, body language, facial expressions, vocalizations, pointing, writing, typing, and picture icons. Find a way. Don't give up. It may take time. Behavior can be a form of communication. However, not all behavior is communication. Some behavior is impulsive, stereotyped, frozen due to seizure activity or difficulty with initiation, or out of a person's conscious control such as a tic. People who have significant motor dyspraxia, which is common in cerebral palsy and autism, may have normal cognition with significant difficulty with speech and other forms of expressive communication.

Speech is a complex motor planning function which requires the coordination of breath and dozens of facial muscles. It utilizes different parts of the brain than other language functions such as reading, encoding and retrieving memories, vision, and hearing. No assumptions can be made about a person's cognition based upon their inability to produce clear speech. Cognition can't be assessed accurately in people who do not have a fluent form of expressive communication. When working with nonspeaking patients, ask how to best to support their communication. Give time for them to respond without interrupting, even if their response is delayed or slow. Presume that your patient understands or can learn. Speak to your patient in a normal tone, volume, and speed unless directed to make accommodations. If you are uncertain how much a patient is understanding, make sure they can see and hear you and you are using their preferred language. Speak to them directly rather than to their supporters. Ask permission to get additional information from others. Give them the same information you normally would provide to any patient. Provide information in a variety of formats such as verbally, visually, and through demonstrations or practice. Nonspeaking people should receive assessments to determine the best augmentative and alternative communication strategies [10].

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Psychoeducational or Neuropsychological Assessments

Children ages 3–21 are entitled to a free, appropriate education in the least restrictive setting [11]. Many people with developmental disabilities, including those with intellectual disabilities, are pursuing higher education or are employed. Psychoeducational and neuropsychiatric testing can help identify and build on strengths and suggest adaptations and modifications to enhance learning. Educational and vocational outcomes are better when people are included in general education classrooms and workplaces [12, 13].

Effective Communication with Families

Tips for Breaking Diagnostic News

To help families hear news about a new major diagnosis in a constructive way, start by conveying in your body language, tone, and words that you genuinely like your patient. For example, you can put a small child on your knee or cuddle them in your arms, give them a warm smile or a tickle, and compliment the family's parenting. Be straightforward about the results of tests or evaluations. Avoid language or tone that implies that being disabled is bad or tragic. Most people with disabilities rate their quality of life similarly to nondisabled people. Expressing pessimism about quality of life or suggesting that living with a disability is suffering can lead to decisions which limit life sustaining care or opportunities and can easily become a self-fulfilling prophesy. Life expectancy and outcomes continue to improve for people with disabilities and encourage patients to connect to disability organizations which can provide patients with positive role models. Share your patient's hopes, your uncertainty, and the range of likely medical issues and outcomes. Assure the family that you will be there for them to help their child maximize their potential and help to connect them to support no matter what happens on their journey.

Practical Problem-Solving

Some families go through a grieving process where they mourn the child they thought they were going to raise and adjust to parenting a child with a disability. If parents express grief and disappointment, encourage them to get counseling so they have an appropriate time and space to work through their feelings without negatively impacting their child by expressing those feelings in front of them. Redirect the conversation to practical problem-solving and next steps.

Caregiver Assessment and Support

People with disabilities have a right to maximize their potential. So do their caregivers. Both are important. Most families find caring for a child with a disability to be very rewarding. However, if caregivers are feeling isolated, overwhelmed, burnt out, or resentful of their role, in a separate visit, assess their needs. Win-win solutions are usually possible. If caregivers feel they are not able to pursue their own goals, a meeting with a social worker or developmental services care coordinator may be necessary to develop a more sustainable service and support plan for the family. All caregivers need respite, and some caregivers may need to transfer some of their responsibilities to someone else.

Early Intervention

Children ages 0–3 are entitled to assessment and early intervention services. Every state and territory in the United States has a free or reduced cost program to provide services and supports to help babies and toddlers learn new skills and increase their success. The services may include speech, physical, behavioral therapy, infant stimulation, and respite care. It may also include durable medical equipment, adaptive equipment such as wheelchairs and voice output devices for those who are unable to produce speech [14].

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Prevention and Treatment of Co-occurring and Secondary Conditions

Developmental disability is not a disease, but people with disabilities have high rates of co-occurring chronic medical conditions such as seizure disorders, arthritis, occult fractures, and psychiatric conditions. Due to sensory, cognitive, and communication challenges, illness may present in atypical ways. As a result, it may not be recognized until later in the disease process. Illness often presents as a change in function or behavior. Careful documentation of a patient's baseline behavior and function will aide in recognizing changes which indicate disease. A proactive approach to identifying undiagnosed or undertreated conditions is necessary. People with developmental disabilities should have more frequent routine visits to document baseline exam and screen for changes.

Secondary conditions are not a part of a person's disability but result from poor management of risk factors. They include things like pressure sores, aspiration pneumonia, bowel obstructions, injuries and falls, and urinary tract infections. Pressure sores can result from poorly fitted wheelchairs, pressure points on mattresses, lack of sufficient personal assistance to reposition, or skin breakdown from incontinence and poor hygiene. Aspiration pneumonia can result from unrecognized dysphagia, inappropriate food textures, positioning, or rushing when feeding. Bowel obstruction and urinary tract infections can result from poorly managed constipation. Injuries can be avoided with proper mobility devices or personal assistance, helmets or hip padding for people with generalized seizure disorders, and careful training and procedures for lifting during transfers and transportation.

Abuse and Neglect/Trauma

People with developmental disabilities are at high risk of all types of abuse including physical, emotional, sexual, and financial. They are also at risk for all types of human trafficking including child sex trafficking which is the fastest growing type of crime in the United States [15]. Family physicians should have a high index of suspicion and fulfill obligations to report any suspected mistreatment. Provide information to patients about healthy sexuality.

Trauma-informed principles should be used. Avoid physical restraint of teenagers and adults. This is often traumatizing and can lead to injuries of both patients and staff. If necessary, use sedation for medical procedures. It is not unusual for providers to ignore or downplay the agency of a disabled individual when a medical procedure is required. Providers may be tempted to accept proxy consent from a parent or conservator for physical restraint for a medical procedure. This practice is ethically questionable, at best. In all but the most urgent situations, if a patient is unable to consent, use patience and sedation if necessary. Along the same lines, consent is always required in order to touch patients or their adaptive equipment. Provide patients with information about sexual health. Respect and encourage patients to set boundaries about how and by whom they are touched [16].

Transition to Adulthood

Transition is a process, not an event. Transitions involve people, activities, and locations. The major things that provide stability in our lives are our home, major relationships, and activities such as school or work. Try not to make major changes in more than one of these at once. Start preparing children early to take increasing control of their relationships with their health care providers, personal assistants, and education. Supported decision-making is an alternative to guardianship which allows people with disabilities to retain their legal capacity to direct their lives, even if they need support from people they trust to make decisions. Encourage families to prepare children with disabilities to direct their own lives. To assist with preparing for adult life, children with disabilities should have opportunities to communicate with health professionals and service providers directly. Educate people with developmental disabilities about their conditions.

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They should be included in meetings where information about them will be discussed or decisions that impact them are made. Provide them with opportunities to make decisions. If transitions to new health care providers will be needed, try to stagger changes as much as possible to maximize continuity [17].

Aging with a Developmental Disability

The service needs of people with developmental disabilities may become more intense as they age, and families may not be able to provide the same level of support. While children get regular assessments through the school system, adults may need referrals or help to get functional assessments as their service needs evolve. Ideally, changing service needs should not lead to loss of home and the important relationships people with disabilities form with members of their household. Skilled nursing supports, additional personal assistance, home modifications or adaptive equipment, and when medically appropriate, access to palliative care and hospice should be made available to enable people with developmental disabilities to age in place.

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Part VIII

Allergy

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Common Allergic Disorders

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M. Jawad Hashim

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Allergic Rhinitis

General Principles

Definition and Background

Allergic rhinitis is a disease characterized by clear nasal discharge, nasal itching, sneezing, and airflow obstruction, due to IgE-mediated inflammatory reaction in sensitized persons. Fatigue and malaise may occur concomitantly, leading to common labels such as "hay fever" or simply "allergies." Allergens most commonly implicated in allergic rhinitis include plant pollens, dust mites (*Dermatophagoides*), pet (cat, dog) dander, and house pests like cockroaches. Coexisting conditions include asthma, allergic conjunctivitis, atopic dermatitis, and obstructive sleep disorders. Allergic rhinitis, asthma, and atopic dermatitis are sometimes referred to as the "atopic triad." Despite being a very common disorder, allergic rhinitis remains undertreated worldwide [1].

Epidemiology

Allergic rhinitis is a highly prevalent condition that affects 15–50% of the population [2]. Disease onset starts after infancy, rising in early childhood, peaking in adolescence, and decreasing gradually in older age groups [3].

Risk factors include exposure to smoking, family history of allergic diseases, indoor and outside air pollution (living in an urban or industrial area), furry pets, carpeted floor, cockroaches, and antibiotic use [2, 4].

Due to its high prevalence, allergic rhinitis is a leading cause of productivity loss at work and school. The direct costs in the United States alone exceed US$11 billion per year, a majority

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of which are drug prescriptions [5]. Allergic rhinitis is perhaps the cause of greater loss of productivity than any other disease.

Classification

Allergic rhinitis can be classified as intermittent or persistent. Allergic rhinitis is considered intermittent if exposure or symptoms occur less than 4 days per week or less than 4 weeks per year. If exposure or symptoms exceed these durations, the term persistent allergic rhinitis is applied. This distinction between intermittent and persistent helps guides treatment selection.

Clinical severity of allergic rhinitis is graded into two levels: (1) mild and (2) moderate-to-severe. The moderate-to-severe level is associated with asthma as well as sensitization to dust mite, pollen, and cat dander [6]. The use of previous classification into seasonal and perennial subtypes is now discouraged as these clinical descriptions are overlapping.

Disease coding into subcategories by specifying the triggering allergen aids in accurate diagnosis and treatment. Thus, allergic rhinitis may be coded as due to pollen, food, animal (cat or dog) hair and dander, and other allergen or, if allergen remains unknown, as unspecified. In patients with coexisting bronchial asthma, listing asthma as the primary diagnosis is recommended.

Approach to the Patient

The diagnostic approach to the patient with suspected allergic rhinitis relies on careful medical interviewing with additional supporting information from physical examination and allergen testing. In patients who report identifiable triggers or have seasonal symptoms and exhibit a clinical response to antihistamines or nasal steroid sprays, the diagnosis of allergic rhinitis is straightforward. More commonly, patients may not have a clearly identifiable trigger. Coexisting allergic disorders such as atopic dermatitis and asthma as well as a family history of these or allergic rhinitis itself increase the likelihood of allergic rhinitis.

Diagnosis

History

The chief symptoms of allergic rhinitis are nasal congestion, watery nasal discharge, nasal itchiness, and sneezing. Associated symptoms include posterior discharge of nasal secretions (postnasal drip), sniffling, and itching in eyes. Patients may be able to identify triggering allergens that provoke episodes of rhinitis, such as exposure to pet dander from cats or dogs. Others may indicate certain seasons coinciding with pollen production; however, year-round pollen production can lead to persistent symptoms.

Patients may report problems caused by posterior nasal discharge (postnasal drip). These troublesome symptoms include spasmodic cough, frequent throat clearing, coughing spells when speaking, and a sensation of choking. Allergic rhinitis affects sleep quality leading to insomnia, restless sleep, disordered breathing, nocturnal enuresis, snoring, as well as daytime sleepiness [7]. Hyposmia can occur with longstanding allergic rhinitis.

Physical Examination

Findings suggestive of allergic rhinitis include clear nasal discharge and pale discoloration of the nasal mucosa. Nasal turbinates may appear swollen and boggy with a pale bluish or pink appearance. Nasal septal perforation may occur due to inappropriate technique in using nasal steroid sprays or less common causes, such as Wegener's granulomatosis. Eyes may show conjunctival hyperemia with watery discharge. Children may exhibit darkening of periocular areas with mild puffiness termed "allergic shiners," attributed to congestion in the veins of the eyelid. Repeated upward rubbing of the nose may produce a horizontal skin crease over the nose. Physical examination may uncover coexisting asthma and atopic dermatitis.

Laboratory and Imaging

Plain radiographs of the sinuses are not recommended. Radiological imaging does not provide any specific diagnostic information relevant to

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allergic rhinitis. Imaging of the nasal sinuses and adjoining structures via computed tomography (CT) or magnetic resonance imaging (MRI) may be indicated when complicated chronic sinusitis with extension of infection, nasal polyposis, or a neoplasm is suspected.

Special Testing

Allergy to an antigen is a clinical diagnosis. Proof of allergen sensitivity is not needed to start empiric treatment in patients with a likely diagnosis of allergic rhinitis. A positive skin or blood test, without symptoms of allergy, does not necessarily denote that the patient has an allergy to that antigen. Allergen sensitization testing is indicated when the response to 2–4 weeks of moderate intensity anti-allergy treatment is inadequate; when the diagnosis is unclear to guide therapeutic adjustments; or when knowledge of the specific allergens involved could alter treatment recommendations. Selection of specific antigens during testing should be guided by patient's history, rather than obtaining an indiscriminate battery of tests.

Either laboratory blood testing or office-based skin testing can provide proof of sensitization to specific allergens. Both methods are considered to have similar accuracy; however, skin testing may have higher sensitivity. Furthermore, each of these two alternatives has certain benefits over each other. With blood testing, there is no risk of anaphylaxis, skin conditions such as atopic dermatitis and dermatographism can be ignored, patients can continue taking antihistamines, and skill and special equipment needed to perform skin testing are not needed. On the other hand, skin testing yields results promptly and is also less expensive than blood testing. In spite of the forgoing discussion, as discussed above, a majority of patients with allergic rhinitis can be diagnosed and managed without allergen testing.

In skin testing, allergens are introduced into the patient's skin either using the prick (puncture) or, less commonly, intradermal injection and observed for wheal and flare formation in 15–20 min. Intradermal technique is more sensitive and is often used to follow up on negative skin prick testing. Other skin testing methods such as scratch testing are less reliable and are no longer recommended. As skin testing involves introducing antigens that stimulate mast cells to release histamines and other proinflammatory cytokines via IgE binding, allergic adverse reactions including anaphylaxis are potential concerns. Skin testing is therefore contraindicated in patients with severe or uncontrolled asthma as well as any severe illness such as unstable cardiovascular conditions. Current medications should be carefully documented as medications such as antihistamines and tricyclic antidepressants may suppress the skin reaction. Finally, the standardization of allergen extracts and skin testing techniques is essential to ensure reliable results.

Blood testing involves ascertaining the serum for the presence of IgE to a set of specific allergens using an immunoassay. As enzyme-linked immunoassays are more commonly employed, the term "RAST" used to refer to radioactive-labeled assays is becoming obsolete. Sampling nasal mucosal fluid for IgE or other inflammatory markers is not recommended in routine clinical practice. Serum testing for total IgE level and for non-IgE antibodies such as IgG is not helpful in the diagnosis of allergic rhinitis.

Differential Diagnosis

Upper respiratory viral infections such as acute rhinopharyngitis may produce similar symptoms especially rhinorrhea and sneezing but often have additional features such as fever, malaise, muscle aches, and a shorter duration. Recurrent viral infections especially in children should be differentiated from seasonal allergic rhinitis episodes by careful history taking enquiring about the presence of environmental triggers and sick contacts.

Chronic sinusitis, more accurately referred to as chronic rhinosinusitis and a potential consequence of allergic rhinitis, is characterized by thick mucopurulent nasal secretions, unilateral (or sometimes bilateral) nasal discharge, sinus tenderness, and a duration of more than 2 weeks.

Since allergic rhinitis is sometimes difficult to distinguish from nonallergic rhinitis (e.g., vasomotor rhinitis or rhinitis medicamentosa), diagnostic

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uncertainty may remain in many patients. The proportion of nonallergic rhinitis may be as high as 50% of all cases with chronic intermittent rhinitis. However, the exact demarcation between allergic and nonallergic rhinitis remains controversial. Even among patients with allergic rhinitis, inflammatory responses in the nasal mucosa can be experimentally induced by nonspecific stimuli. This observation has led to claims that nonallergic rhinitis may only be a tendency to mucosal hyperresponsiveness rather than a specific disease entity. A careful history may uncover irritant stimuli responsible for nonallergic rhinitis such as smoke, chemicals, temperature changes, and odors.

Unusual symptoms such as unilateral rhinorrhea, persistent anosmia, recurrent epistaxis, unilateral nasal blockage, or headache indicate a more concerning cause such as granulomatous diseases, chronic rhinosinusitis, nasopharyngeal tumors, or a cerebrospinal fluid (CSF) leak.

Treatment

Behavioral and Family Issues

Physicians underestimate the impact of allergic rhinitis on their patients' lives [8]. Reduced cognitive function affecting school and work, impaired decision-making ability, and decreased self-esteem have been reported. Increased rates of learning disorders, attention, and conduct deficits impair children with allergic rhinitis in particular when obstructive sleep disorder and asthma are coexistent.

Environmental Measures

Reducing allergens in the home environment by removal of pets such as cats and dogs and house pests, for example, cockroaches, reduces the levels of the allergens but may have a limited effect on patient symptoms. Complete eradication of the allergen is usually not possible, and even reduction in levels is transient – replenishing within a few days – thereby raising issues of long-term feasibility. Intensive use of multiple methods is somewhat more effective but often impractical. Measures such as frequent washing of pets, HEPA air filtration systems, impermeable vinyl bed covers, acaricides (insecticide sprays against house dust mites), frequent washing of floors, removal of upholstered furniture, and washing bedsheets in hot water at more than 55 °C can reduce allergen levels temporarily but are associated with only transient or no improvement in symptoms.

Medications

Approach to Pharmacologic Treatment and Combination Medication Use

Intranasal corticosteroid sprays are the most effective treatment; however, many patients prefer oral medications (Table 1). Drug combinations are more effective than single drug therapy, but

Table 1 Treatment options for allergic rhinitis

Drug class	Drugs	Efficacy	Main adverse effects and cautions
Oral antihistamines, second generation	Cetirizine, loratadine, desloratadine, fexofenadine	Mild to moderate	Mucosal dryness, sedation
Intranasal steroids	Fluticasone, triamcinolone, budesonide	Moderate	Nasal dryness, epistaxis
Intranasal antihistamines	Azelastine, olopatadine	Mild to moderate	Bitter taste, epistaxis, sedation, burning sensation
Oral decongestants	Pseudoephedrine, phenylephrine	Mild	Agitation, gastrointestinal disturbances, insomnia
Intranasal decongestants	Oxymetazoline	Mild to moderate	Rebound nasal congestion, rhinitis medicamentosa
Oral leukotriene antagonists	Montelukast	Mild	
Immunotherapy	Specific subcutaneous/sublingual allergens	Moderate	Allergic reactions including anaphylaxis

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adding oral antihistamines to nasal corticosteroids does not confer benefit [9]. Leukotriene inhibitors and intranasal antihistamines are less effective than nasal corticosteroid sprays [10]. Intranasal antihistamines have the fastest onset of action (within minutes), while intranasal corticosteroids take a few hours to a few days.

Second-generation antihistamines are recommended for daily use based on high-quality evidence, although intermittent usage can be helpful in seasonal symptoms. Switching to a different antihistamine may sometimes work in patients who are refractory to the initial agent. The choice between oral and nasal antihistamine should be decided on patient preferences since efficacy appears to be similar.

Effectiveness and compliance with standard drug treatment is often modest, and one-third to two-thirds of children and adults have limited or no response. Such cases should be considered for allergen immunotherapy.

Oral Antihistamines

H_1 antihistamines, although only moderately effective, are most commonly used as the first line of treatment in allergic rhinitis primarily because of rapid onset of action, over-the-counter availability, and low cost. Additional benefits include once-daily oral dosing and sustained control with daily intake. These well-established medications have proven efficacy in clinical trials for the relief of rhinorrhea, sneezing, nasal itching, and nasal discharge. Additionally, these agents reduce ocular itching and watery discharge in case of concomitant allergic conjunctivitis. However, antihistamines are less effective than intranasal steroids in the treatment of allergic rhinitis.

Antihistamines are classified into first-generation agents, such as diphenhydramine, chlorpheniramine, and hydroxyzine, and second-generation drugs, for example, loratadine, desloratadine, fexofenadine, and cetirizine, which tend to be nonsedating. Both groups are considered to have similar efficacy in allergic rhinitis. First-generation agents are prone to anticholinergic (muscarinic receptors) adverse effects such as drowsiness and dry mouth. Cetirizine has been shown to be a safe and effective first-line antihistamine in allergic rhinitis [11]. Nasal mucosal dryness can become unpleasant at higher doses. Sedation can affect the ability to drive safely or work in high-risk situations such as at industrial sites. Work performance can be impaired even without drowsiness. In the elderly, cognitive impairment, delirium, blurry vision, dry mouth, constipation, and urinary retention are potential concerns with antihistamine use. Antihistamines should be avoided in children younger than 2 years of age [12].

Intranasal Corticosteroids

Intranasal steroids such as fluticasone, triamcinolone, and budesonide nasal sprays are the most effective treatments available for allergic rhinitis, yet their effectiveness is only moderate, and patients may need additional medications. Different agents in this class of medications appear to have similar efficacy, and the choice may depend on patient experience based on side effects such as aftertaste and odor. These drugs may take 1 week or more to show clinical improvement, and, as in inhalers for asthma, patient counseling about technique of application is important. Patients should be advised to flex the neck forward, keep the spray pointing posteriorly and slightly away from the nasal septum (facilitated by holding the canister in the contralateral hand), and pinch the other nostril while inhaling. Vigorous nasal inhalation and rinsing of nostrils should be avoided immediately afterward. Intranasal steroids are known to help relieve the symptoms of concomitant allergic conjunctivitis and to improve asthma control.

Adverse effects of intranasal corticosteroids include nasal dryness and epistaxis. There appears to be no long-term effects on nasal mucosa, hypothalamic-pituitary axis, bone growth in children, and the ocular lens.

Intranasal Antihistamines

Nasal antihistamines such as azelastine and olopatadine show effectiveness in reducing nasal congestion but may be associated with bitter taste, epistaxis, drowsiness, headache, and burning sensation in the nasal mucosa. A combination

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intranasal spray containing an antihistamine as well as a corticosteroid is superior to intranasal corticosteroid alone [10].

Oral Decongestants

Oral decongestants such as pseudoephedrine are available in combination with antihistamines, typically denoted by the suffix "-D" in the trade name. They improve the modest relief of nasal blockage by antihistamines, but the combination may be associated with excessive mucosal dryness.

Nasal Decongestants

Topical decongestants such as oxymetazoline nasal sprays are effective in reducing nasal stuffiness with an initial dose, an effect that decreases rapidly with continued use within a few days. Concern for rebound nasal congestion, termed rhinitis medicamentosa, with long-term use has led to recommendations for intermittent usage limited to 3 days at a time.

Oral Leukotriene Antagonists

Oral leukotriene receptor antagonists such as montelukast are not recommended as the primary treatment choice in allergic rhinitis due to limited efficacy. Among patients with coexisting asthma, these agents may be more appropriate. Leukotriene inhibitors show enhanced efficacy in allergic rhinitis when they are co-administered with an oral antihistamine.

Immunotherapy

Allergy immunotherapy consists of subcutaneous or sublingual exposure to gradually increasing doses of one or more antigens over 3–5 years. Immunotherapy is efficacious and cost-effective compared to standard drug treatment, and its effects last beyond the treatment course [5]. Apart from the inconvenience of twice weekly injections, allergic reactions including anaphylaxis remain a potential concern. The sublingual route appears to be safer and easier for patients as therapy can be administered at home. Along with improvement in concurrent asthma and allergic conjunctivitis, immunotherapy prevents development of new onset asthma and other allergies.

Referrals

Consultation with an allergy specialist is recommended for patients with allergic rhinitis who are not well controlled after a 2–4-week trial of pharmacologic treatment with combination medications and those with severe disease. In patients with inferior turbinate hypertrophy and inadequate response to medical therapy, referral to an ENT surgeon for surgery may be helpful. Acupuncture may be considered in selected patients based on patient preference [13].

Counseling and Patient Education

Real-world evidence indicates that patients are usually non-adherent to treatment [10]. Most patients self-medicate and use medications as needed when their symptoms return. The vast majority of patients (including allergy specialists with allergic rhinitis) do not follow the physician's recommendations [10].

Patients should be counseled about the potential adverse effects of antihistamines including sedation and impaired decision-making. Patient counseling about appropriate technique, delayed onset of symptom relief, and the importance of regular daily use are critical in ensuring effectiveness of inhaled intranasal steroids.

Prevention

Although some patients report benefit, there is inconsistent evidence for daily nasal rinsing, wearing a face mask outdoors, staying indoors especially in the early morning and after sunset, avoiding lawn mowing and leaf clearing, planting insect-pollinated flowers rather than wind-pollinated ones, drying clothes indoors, shampooing hair to remove pollen, keeping windows closed, or relocating to another geographic area during high pollen season.

The use of impermeable mattress covers from birth onward does not prevent sensitization to dust mites in infants.

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Family and Community Issues

Public health awareness campaigns about allergic rhinitis appear worthwhile given its high prevalence, the availability of low-cost treatment options, as well as the very high burden on school and work productivity.

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Anaphylaxis

39

Alfred C. Gitu and Amy Skiff

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Definition

Anaphylaxis is an acute, severe, potentially life-threatening, multisystem syndrome [1]. It is characterized by the release of mast cell- and basophil-derived mediators into the circulation

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[2]. It manifests as rapidly progressing airway, breathing, or circulatory problem and is usually, although not always, associated with skin and mucosal changes [3].

Biphasic anaphylaxis is recurrence of signs and symptoms occurring 1–72 h after resolution of the initial episode [2].

Epidemiology

Lifetime cumulative prevalence of anaphylaxis is reported as 5.1% in the general US population, when the criteria for diagnosis are defined as involvement of 2 or more systems, together with respiratory or cardiovascular involvement. The prevalence falls to 1.6% if a hospital visit and a threat to the patient's life are added to the above criteria [4]. The reported incidence of anaphylaxis in studies done after 2005 is approximately 50 episodes per 100,000 person-years, but estimates may be susceptible to ascertainment bias [5]. The frequency of anaphylaxis varies by geographic region (higher in areas with less sunlight), demographic group (higher in children age 0–4 years than in adults), cause (food-induced in younger people vs drug-induced and Hymenoptera in older patients), and gender (more frequent in males until 10–15 years, females more after age 15) [5].

An increase in frequency of anaphylaxis over time has been reported in the literature. However, it is debated whether this is due to increased diagnosis or due to a true increase in the frequency of the disease. At least 30% of patients who have survived an episode of anaphylaxis will experience one or more recurrences [5].

The incidence of fatal anaphylaxis ranges from 0.12 to 1.06 deaths per million person-years, while the prevalence of deaths in patients diagnosed with severe anaphylaxis is 0.3%–2% [5]. Drugs, insect stings, and food are the three leading causes of fatal anaphylaxis, with drugs being the trigger in 50% or more of cases. In several studies, food-induced anaphylaxis was more frequently fatal in younger patients (5–35 years) whereby insect- and drug-induced anaphylaxis was more frequently fatal in the older population (>35–40 years) [5]. Older age signals a greater risk of fatal anaphylaxis, potentially due to the reduced capacity to tolerate the effects of hypoxia, hypotension, and arrhythmia.

Pathogenesis

An important mechanism in many cases of anaphylaxis is that of IgE binding and cross-linking of the high affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Anaphylaxis also involves multiple other cell types such as neutrophils, monocytes, macrophages, and platelets as well as signaling through complement components, cysteinyl leukotrienes, platelet activating factor, IL-6, IL-10, and TNF-receptor 1 [2].

The understanding of anaphylaxis has evolved through the use of precision medicine to more of a mechanistic description of phenotypes with underlying endotypes supported by diagnostic biomarkers [6]. As shown in Fig. 1, these phenotypes are defined by clinical presentation into type I-like reactions, cytokine storm-like reactions, and mixed reactions. Several studies have also identified complement-mediated activation of basophils and mast cells as the underlying mechanism in some cases of severe anaphylaxis [6].

The endotypes underlying these phenotypes include IgE- and non-IgE mediated processes, direct mast cell and basophil activation, cytokine release, mixed reactions, and complement activation. Biomarkers that are involved in these processes include histamine, tryptase, and other mediators, as well as cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin-1 beta (IL-1β) [6]. In type I reactions and selected cases of cytokine-release and mixed reactions, desensitization is indicated. However, use of desensitization is not indicated in direct mast cell/basophil release due to complement activation [6].

Triggers

Anaphylactic triggers can provoke a response through IgE- and non-IgE mediated mechanisms (see Fig. 2). The more rapidly anaphylaxis

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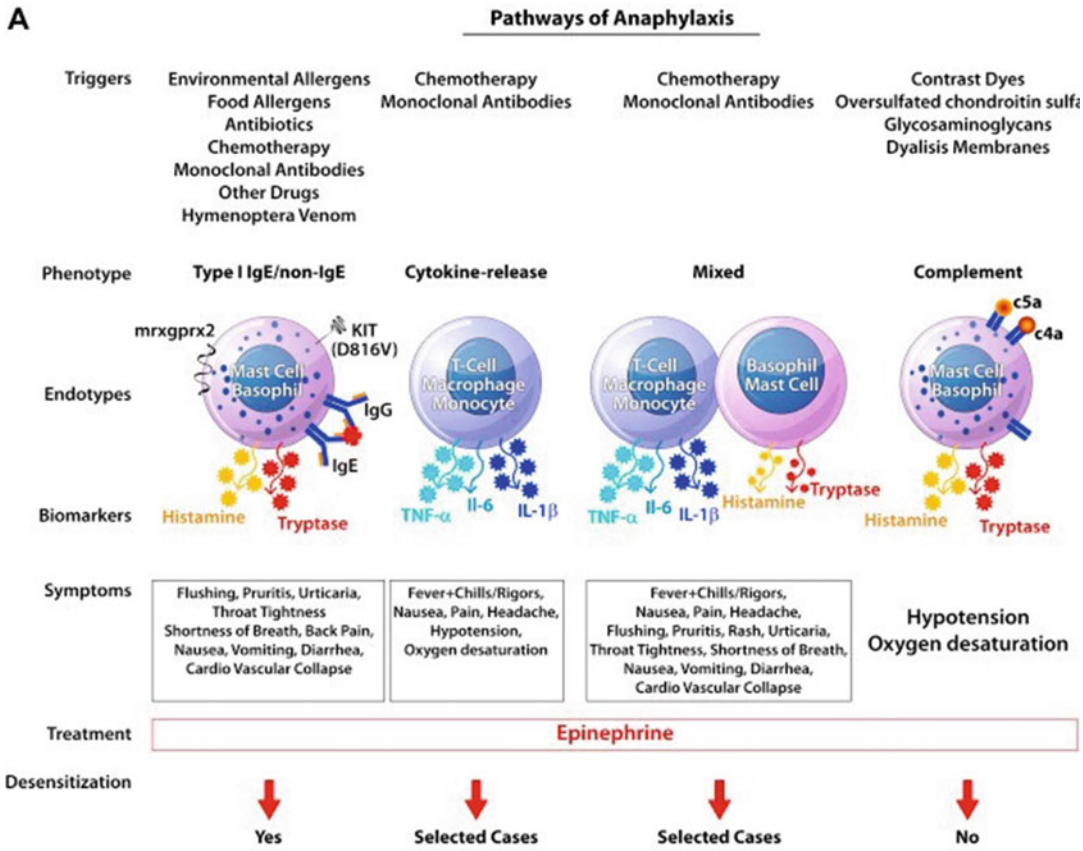


Fig. 1 Modified from [6] Used with permission

develops, the more likely the reaction is to be severe and potentially life threatening [7]. Prompt recognition of signs and symptoms of anaphylaxis is critical, and epinephrine should be administered as soon as anaphylaxis is suspected.

Food

Food is the leading cause of anaphylaxis presenting to United States emergency departments and is estimated to affect up to 8% to 11% of the US population [2]. Foods most commonly responsible for anaphylaxis include peanuts, tree nuts, shellfish, fish, milk, and egg, although any food can produce a reaction [8]. Allergy testing to foods should be considered for anyone who has experienced an anaphylactic event [8]. Patients at high-risk for fatal food-induced anaphylaxis include adolescents, patients with a prior history of a reaction, patients allergic to peanuts or tree nuts, patients with a history of asthma, and those presenting with the absence of cutaneous symptoms [8]. Special care must be taken by patients, parents, and caretakers to investigate the ingredients and contents of foods to prevent trigger-food ingestion by a patient with a known food allergy. They should also pay close attention to food advisory labeling (e.g., "may contain") which has become more prevalent. This avoidance strategy is the cornerstone of prevention for food-induced anaphylaxis.

Medications

Medications rival food as the most common cause of anaphylaxis [8]. The most common implicated classes are antibiotics, especially

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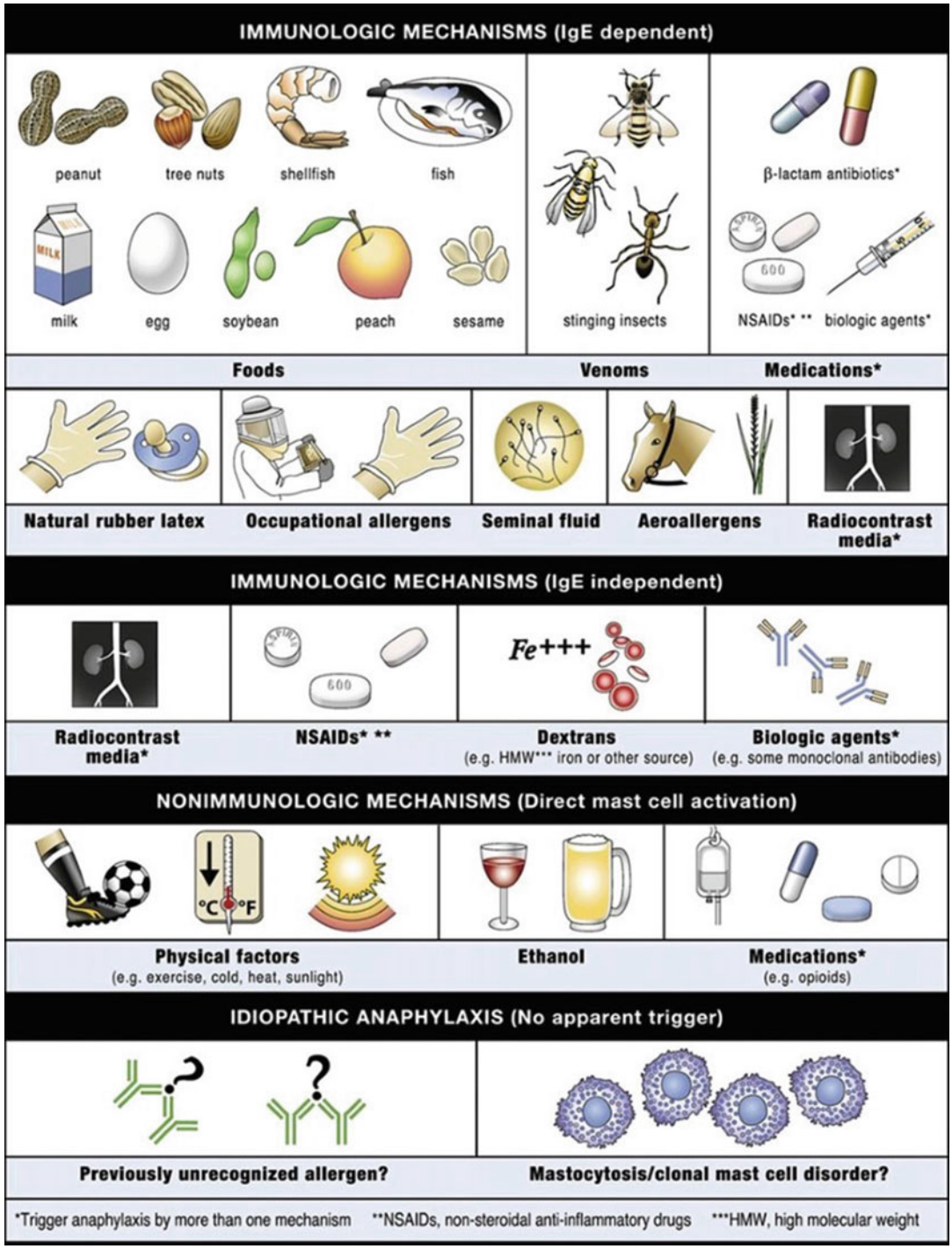


Fig. 2 Anaphylaxis mechanisms and triggers. (Adapted with permission from Elsevier [10])

β-lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDS). Approximately 10% of the US population has reported allergies to penicillin. Higher rates have been reported by older patients and those that are hospitalized. However, the risk of clinically significant

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IgE-mediated or T lymphocyte-mediated penicillin hypersensitivity is less than 5%. IgE-mediated penicillin allergy diminishes over time, with 80% of patients becoming tolerant after 10 years [9].

In patients with penicillin allergy, cross-reactivity with cephalosporins occurs in approximately 2% of cases. However, in the subset of patients with a history of anaphylaxis after penicillin administration, around 40% have shown cross-reactivity with a cephalosporin, but this is almost exclusively with the aminocephalosporins (e.g., cefaclor, cephalexin, cefadroxil) that have similar chemical side chains or R_1 groups [9].

For patients with medium to high risk penicillin allergy histories, penicillin skin testing and referral to an allergist/immunology specialist for evaluation should be considered. Negative penicillin skin testing results carry a predictive value exceeding 95%. This approaches 100% when combined with an oral amoxicillin challenge [9].

NSAIDS are another common cause of anaphylaxis. True anaphylactic reactions appear to be specific to each NSAID. The majority of those who have experienced an anaphylactic reaction to one NSAID can tolerate a structurally unrelated NSAID [8].

Venoms

Anaphylaxis from insect stings differs clinically in children and adults. Cutaneous symptoms are the most common overall, affecting 80%; they are the sole manifestation in 15% of adults but in more than 60% of affected children [10]. Systemic reactions are reported by up to 3% of adults and 1% of children. Patients with anaphylactic reactions to an insect sting should be referred for skin testing to venom if the insect was a flying hymenoptera (e.g., bees and wasps) and to whole-body extract if the insect was a fire ant [8]. Venom immunotherapy for flying hymenoptera is 90–98% effective in preventing further anaphylactic reactions. Any patient experiencing anaphylaxis to a hymenoptera sting should have a baseline serum tryptase drawn to rule out systemic mastocytosis [8].

In addition to allergy referral, patients should be counseled on avoidance of the offending insect and prescribed an auto-injectable epinephrine with counseling on proper use.

Anesthesia/Perioperative

The precise incidence of anaphylaxis related to anesthesia is unknown. Clinical experience suggests that it is more commonly seen with general anesthesia (with an incidence of 1:10,000 to 1:20,000) than with local or spinal anesthesia [8]. The most frequent causes in the perioperative period are neuromuscular blocking agents and antibiotics [8]. However, other agents have also been implicated, such as barbiturates, opioids, blood products, and latex [8]. Management of anaphylaxis in the perioperative period is similar to anaphylaxis in other situations.

Exercise

Exercise-induced anaphylaxis (EIA) and food-dependent EIA (FDEIA) are rare but potentially life-threatening syndromes in which the association with exercise is the key defining characteristic [8]. The range of physical activity that triggers the syndrome is broad and EIA is not fully reproducible. In FDEIA, the combination of ingesting sensitizing food and exercise is required to induce symptoms [8]. Anaphylaxis occurs within a few hours of specific food ingestion and exercise, with wheat and omega-5 gliadin as the predominant triggers [6]. However, other grains, nuts, and seafood have also been reported [8].

The management of EIA must be tailored depending on the severity of symptoms, presence of co-triggers, and the patient's desire to continue to exercise. Patients must carry two epinephrine auto-injectors while exercising and stop exercising immediately at the onset of symptoms. Prophylactic treatment with corticosteroids and antihistamines is not consistently effective and often fails to prevent attacks [8].

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Diagnosis

The diagnosis of anaphylaxis should be made clinically. The National Institute of Allergy and Infectious Diseases proposed clinical criteria that have a sensitivity of 95% and specificity of 71% in an emergency department setting [1, 2]. Diagnosis and treatment of anaphylaxis must occur rapidly and should not be delayed for confirmatory testing, which has poor sensitivity [11].

Clinical Criteria [1]

1. Acute onset of illness with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue, or uvula) and at least one of the following:
   (a) Respiratory compromise (e.g., dyspnea, bronchospasm, stridor, hypoxemia).
   (b) Reduced blood pressure or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen (for that patient):
   (a) Skin/mucosal involvement.
   (b) Respiratory compromise.
   (c) Reduced blood pressure.
   (d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced blood pressure (BP) after exposure to a known allergen.
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP.
   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

History

An extensive history from the patient, family member, or witness should be obtained (See below) [8]. Infants, teenagers, pregnant women, and the elderly are at higher risk for serious reactions [11]. Other risk factors for severe anaphylaxis include asthma, atopy, and cardiovascular disease and potentially mast cell disorders, beta-blocker, or angiorctensin-converting enzyme inhibitor use [12].

Essential History to Obtain in the Evaluation of a Patient with an Anaphylaxis Episode

- Detailed history of ingestants (foods/medications) taken within 6 h before the event.
- Activity in which the patient was engaged at the time of the event.
- Location of the event (home, school, work, indoors/outdoors).
- Exposure to heat or cold.
- Any related bite or sting.
- Time of day or night.
- Duration of the event.
- Recurrence of symptoms after initial resolution.
- Exact nature of symptoms (e.g., if cutaneous, determine whether flush, pruritis, urticaria, or angioedema).
- In a woman, the relation between the event and her menstrual cycle.
- Was medical care given and what treatments were administered.
- How long before recovery occurred and was there a recurrence of symptoms after a symptom-free period.

Physical Exam

The evaluation should initially focus on patient stability and vital sign assessment, but then examination should shift to potentially involved organ systems. This should include lung and cardiac auscultation, assessment of tissue perfusion, abdominal exam, skin exam, cognitive assessment, and inspection of the throat and mucous membranes. The frequency of clinical manifestations is depicted in Table 1 [8].

Ancillary Studies

Treatment with epinephrine for a suspected case of anaphylaxis should not be delayed for laboratory studies. However, certain tests may be

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Table 1 Clinical manifestations of anaphylaxis

Frequency of clinical manifestations	Percentages
Abdominal	
Nausea, vomiting, diarrhea, cramping	25–30
Cutaneous	
Urticaria and angioedema	62–90
Flushing	45–55
Pruritus without rash	2–5
Dizziness, syncope, hypotension	30–35
Respiratory	
Dyspnea, wheeze	45–50
Upper airway angioedema	50–60
Rhinitis	15–20
Miscellaneous	
Headache	5–8
Substernal pain	4–5
Seizure	1–2

[a]Adapted from [8]. Used with permission

considered in working up the differential diagnoses of anaphylaxis [11].

1. Serum tryptase –levels peak 60–90 min after the onset of symptoms and persist for 6 h.
2. Plasma histamine –levels begin to rise within 5–10 min and remain elevated for less than 60 min.
3. Plasma-free metanephrine and/or urinary vanillymandelic acid may be used if a paradoxical response to a pheochromocytoma is suspected.
4. Serum serotonin can help rule out carcinoid tumor.

Differential Diagnosis

The differential diagnosis of anaphylaxis is summarized in Table 2 [13]. Specific signs and symptoms of anaphylaxis may be seen in other disorders such as urticaria/angioedema and asthma [7].

Management of Anaphylaxis

The treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing, and circulation [1]. When any of the criteria of anaphylaxis are fulfilled, or if there is any other reason to suspect that a patient is experiencing anaphylaxis, epinephrine should be administered immediately. Other resuscitative therapies should also be instituted as needed, including supplemental oxygen for patients with hypoxemia or respiratory symptoms, and intravenous fluids for patients with hypotension [1].

Primary Treatment

Epinephrine is the first-line treatment for anaphylaxis and should be administered as soon as a diagnosis of anaphylaxis is suspected into the anterolateral thigh in a dose of 0.01 mg/kg to a maximum of 0.5 mg in adults and 0.3 mg in children [1, 2]. The dose should be repeated every 5–10 min as needed for refractory symptoms.

Auto-injectors are commercially available in 0.3 mL (0.3 mg) and 0.15 mL (0.15 mg) doses. Per the package insert, the 0.3 mg dose is intended for patients who weigh more than 30 kg and the 0.15 mg dose is intended for patients who weigh 15–30 kg [14]. There have been no published dose-response studies documenting the optimal dose of epinephrine. The 2015 Anaphylaxis Practice Parameter Update recommends that it would seem advisable to consider prescribing an

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Table 2 Differential diagnosis of anaphylaxis

Common diagnostic dilemmas	**Flush syndromes**
Acute asthma[a]	Perimenopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Automatic epilepsy
Acute generalized urticaria[a]	Medullary carcinoma of the thyroid
Aspiration of a foreign body	**Nonorganic disease**
Cardiovascular (myocardial infarction[a], pulmonary embolus)	Vocal cord dysfunction
	Hyperventilation
Neurologic events (seizure, cerebrovascular event)	Psychosomatic episode
Postprandial syndromes	**Shock**
Scombroidosis[b]	Hypovolemic
Pollen-food allergy syndrome[c]	Cardiogenic
Monosodium glutamate	Distributive[d]
Sulfites	Septic
Food poisoning	**Others**
Excess endogenous histamine	Nonallergic angioedema
Mastocytosis/clonal mast disorders[e]	Hereditary angioedema types I, II, and III
Basophilic leukemia	ACE inhibitor-associated angioedema
	Systematic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

Adapted with permission from Elsevier [10]

[a]Acute asthma symptoms, acute generalized urticarial, or myocardial infarction symptoms can also occur *during* an anaphylactic episode

[b]Histamine poisoning from fish, for examples, tuna that has been stored at an elevated temperature; usually, more than one person eating the fish is affected

[c]Pollen-food allergy syndrome (oral allergy syndrome) is elicited by fruits and vegetables containing various plant proteins that cross-react with airborne allergens. Typical symptoms include itching, tingling, and angioedema of the lips, tongue, palate, throat, and ears after eating raw, but not cooked, fruits and vegetables

[d]Distributive shock may be due to anaphylaxis or to spinal cord injury

[e]In mastocytosis and clonal mast cell disorders, there is an increased risk of anaphylaxis; also, anaphylaxis may be the first manifestation of the disease

epinephrine auto-injector in children who weigh less than 15 kg (33 pounds) [8].

As a nonselective adrenergic agonist, epinephrine works rapidly to increase peripheral vascular resistance through vasoconstriction, to increase cardiac output, to reverse bronchoconstriction and mucosal edema, and to stabilize mast cells and basophils.

Antihistamines (H_1-and H_2-antagonists) are considered second-line treatment for anaphylaxis, given their slow onset of action and inability to stabilize or prevent mast cell degranulation or to target additional mediators of anaphylaxis. Unlike epinephrine, antihistamines will not effectively treat cardiovascular and respiratory symptoms such as hypotension or bronchospasm. Antihistamines are useful for the symptomatic treatment of cutaneous symptoms such as urticaria and pruritus.

Although glucocorticoids are frequently used as an adjunctive therapy for anaphylaxis, evidence is lacking to support clinical benefit, and they should not be administered in place of epinephrine in the treatment of acute anaphylaxis [2].

Secondary Treatment

After the treatment of an anaphylactic reaction, an observation period should be considered for all patients for at least 1 h after signs and symptoms have resolved because the reaction might recur as the effect of epinephrine wears off [1]. The recurrence of biphasic reactions occurs in 3–18% of

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anaphylactic reactions [15]. There are no reliable clinical predictors to help identify patients at increased risk for a biphasic reaction, but severity of initial symptoms and/or the administration of >1 dose of epinephrine have been suggested as a guide to determining a patient's risk for developing biphasic anaphylaxis. Additional risk factors include wide pulse pressure, unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug trigger in those younger than 18 years [2].

A reasonable length of time to consider observing the postanaphylactic patient is 4–6 h in most patients, with prolonged observation times or hospital admission for patients with severe or refractory symptoms. More caution should be used in patients with reactive airway disease because most fatalities associated with anaphylaxis occur in these patients [1].

Glucocorticoids and antihistamines are not recommended as an intervention to prevent biphasic anaphylaxis, but may be considered for the secondary treatment of anaphylaxis. In particular, antihistamines are effective therapy for the many cutaneous signs and symptoms associated with anaphylaxis including pruritus, flushing, and urticaria [16].

Discharge Plan

After diagnosis and treatment of anaphylaxis, all patients should be kept under observation until symptoms have fully resolved. They should receive education on anaphylaxis and risk of recurrence, trigger avoidance, self-injectable epinephrine education, referral to an allergist, and be educated about thresholds for further care.

Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. The patient's medical history should be updated to include an electronic flag or sticker regarding their history of anaphylaxis and the trigger(s). The patient can also be instructed to wear and/or carry identification denoting the condition and can also be instructed to have telephone numbers for paramedic rescue squads and ambulance services on hand. A written action plan can be helpful in this regard.

Before discharge, consider measuring allergen-specific IgE levels in serum for assessment of sensitization to relevant allergens ascertained from the history of the anaphylactic episode.

Follow-up Plan

Follow-up with an allergist/immunology specialist is required, particularly for patients in whom the trigger is not known. Allergy/immunology specialists play a uniquely important role in preparing the patient for self-treatment in the community, confirmation of the trigger of an anaphylactic episode, education regarding allergen avoidance, and immune modulation.

Prevention

Patient education is the most important strategy to prevent recurrent anaphylaxis. The first step is that of identification of and avoidance of triggers whenever possible.

Pharmacologic prophylaxis with antihistamines and/or glucocorticoids should be administered to prevent index hypersensitivity reactions to certain chemotherapeutic agents and in patients receiving allergen immunotherapy. Such prophylaxis is not recommended for patients with prior radiocontrast hypersensitivity reactions when re-administration of a low or iso-osmolar, nonionic radio-contrast media agent is required [2].

Immunotherapy may be used, particularly for allergens that are difficult to avoid. Subcutaneous venom immunotherapy protects up to 90% of adults and 98% of children against anaphylaxis from future stings. When necessary, desensitization using a published protocol may be conducted to prevent medication-triggered anaphylaxis [17].

For patients with frequent episodes of unknown or idiopathic anaphylaxis: consider glucocorticoid and nonsedating H_1-antihistamine prophylaxis for 2–3 months; consider measurement of a baseline tryptase level to identify mastocytosis/clonal mast cell disorders [17].

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Anaphylaxis Emergency Action Plan

Patient Name:_____ **Age:**_____

Allergies:_____

Asthma ☐ **Yes** ***(high risk for severe reaction)*** ☐ **No**

Additional health problems besides anaphylaxis:_____

_____

Concurrent medications:_____

_____

Symptoms of Anaphylaxis

MOUTH	**itching, swelling of lips and/or tongue**
THROAT*	**itching, tightness/closure, hoarseness**
SKIN	**itching, hives, redness, swelling**
GUT	**vomiting, diarrhea, cramps**
LUNG*	**shortness of breath, cough, wheeze**
HEART*	**weak pulse, dizziness, passing out**

Only a few symptoms may be present. Severity of symptoms can change quickly.
****Some symptoms can be life-threatening. ACT FAST!***

Emergency Action Steps - DO NOT HESITATE TO GIVE EPINEPHRINE!

1. Inject epinephrine in thigh using (check one):

☐ **Adrenaclick (0.15 mg)** ☐ **Adrenaclick (0.3 mg)**

☐ **Auvi-Q (0.15 mg)** ☐ **Auvi-Q (0.3 mg)**

☐ **EpiPen Jr (0.15 mg)** ☐ **EpiPen (0.3 mg)**

Epinephrine Injection, USP Auto-injector- authorized generic
☐ **(0.15 mg)** ☐ **(0.3 mg)**

☐ **Other (0.15 mg)** ☐ **Other (0.3 mg)**

Specify others: _____

IMPORTANT: ASTHMA INHALERS AND/OR ANTIHISTAMINES CAN'T BE DEPENDED ON IN ANAPHYLAXIS.

2. Call 911 or rescue squad (before calling contact)

3. Emergency contact #1: home_____ **work**_____ **cell**_____

Emergency contact #2: home_____ **work**_____ **cell**_____

Emergency contact #3: home_____ **work**_____ **cell**_____

Comments: _____

_____

_____
Doctor's Signature/Date/Phone Number

_____
Parent's Signature (for individuals under age 18 yrs)/Date

This information is for general purposes and is not intended to replace the advice of a qualified health professional. For more information, visit www.aaaai.org. © 2017 American Academy of Allergy, Asthma & Immunology 4/2017

Fig. 3 Anaphylaxis emergency action plan

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Confirmation of Anaphylaxis Triggers

This is usually performed by an allergy/immunology specialist, who perform skin tests and measure specific IgE levels in the patient's serum. These tests do not distinguish between sensitization associated with increased risk of anaphylaxis, which is relatively uncommon, and asymptomatic sensitization, which is widespread; therefore, the allergens selected for testing should be relevant to the history of the anaphylactic episode [17] (Fig. 3).

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Part IX

Infectious Diseases

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Epstein-Barr Virus Infection and Infectious Mononucleosis

40

Sahil Mullick

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General Principles

Background

The Epstein-Barr virus (EBV) is a member of the Herpesviridae virus family. Humans are the primary reservoir for EBV that targets B-lymphocytes and nasopharyngeal epithelial cells [1]. EBV has a latency phase where, following a primary infection, it infects epithelial cells, enters the circulating B lymphocyte, and persist for the life in a latent

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state [2]. It is the most common causative agent of infectious mononucleosis (IM) [3]. Oral route is the primary method of transmission, attributing to the moniker "the kissing disease." There is also evidence of mutation in EBV being linked to certain types of cancers in humans [4].

Epidemiology

EBV, with more than 90% seroprevalence, is one of the most common viral infections in the world. In developing countries and people living in lower socioeconomic groups, most EBV transmission occurs in infancy and early childhood with the primary infection being asymptomatic. In the industrialized countries and members of the higher socioeconomic groups, EBV causes IM primarily among adolescents and young adults, The annual incidence of IM in the United States is estimated to be 0.5%, with the estimated annual IM incidence rates for young adults, which varies widely, ranging from about 0.2% to 0.8% for ages between 15 and 19 years [5]. This variation could be due to differences in populations studied, true geographic or epidemiologic variation, or variations due to sample size. There is no gender predisposition, yearly cycle, or seasonal variation in IM [6].

Classification

At present, EBV isolates worldwide can be grouped into Type 1 and Type 2, a classification based on variations in the virus' genetic sequence, with Type 1 EBV most prevalent worldwide and Type 2 EBV more common in parts of Africa [7]. This genome variation is important as it may contribute to some of the diseases associated with EBV.

Approach to the Patient

EBV-induced IM should be suspected when an adolescent or young adult complains of sore throat, fever, and malaise and also has pharyngitis and lymphadenopathy. An algorithmic approach can be used [8], especially when considering IM-like illnesses in the differential diagnosis to ensure that conditions warranting specific therapy are distinguished from others requiring only supportive care [9].

Diagnosis

History

The natural history of IM is highly variable, owing to differences in patient populations, criteria used for diagnosis, and methods used for description, and majority of the patients recover without apparent sequelae [6]. EBV has an incubation period of approximately 30–50 days, and whether an individual develops IM depends on the timing of exposure to the virus. Children often present with nonspecific or no symptoms. Young adults tend to present with sore throat, fever, fatigue, and malaise. An older age at infection is generally considered a risk factor for severe EBV primary infection [10]. Cough, rash, arthralgias, myalgias, nausea, and somnolence are unusual symptoms, present in $<10\%$ of patients [11].

Physical Examination

Pharyngitis, fever, and lymphadenopathy constitute the classic triad of presenting signs, occurring in over 80% of patients with IM. Splenomegaly may not be detectable upon physical examination, but ultrasound assessment of splenic size during acute IM has shown that all patients develop splenomegaly of varying degrees [12]. Splenic rupture should be suspected in a patient presenting with classic IM, abdominal pain, and anemia. Other clinical findings may include pharyngeal inflammation and palatal petechiae, seen more commonly in adolescents. Jaundice and hepatomegaly tend to occur more frequently in older adults [13]. Patients with IM, who were presumed to have strep throat and given a penicillin derivative such as amoxicillin for treatment, may also present with a typical copper-colored maculopapular rash. This is thought to be due to transient penicillin

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hypersensitivity induced by immune dysregulation during the acute stage of infection [14].

Rarely, patients with primary EBV infection may develop chronic multisystem disease with two clinical patterns. The first and more common is recovery from the initial disease but persistent lingering or recurring symptoms that develop months to years later, and the second pattern is a continuous "mono-like" illness that may last indefinitely [14].

Acute EBV infection has been associated with complications such as meningitis, encephalitis, Guillain-Barre syndrome, aplastic and autoimmune hemolytic anemia, myocarditis, pneumonitis, and nephritis [15]. Other conditions, such as lymphoproliferative disorders, connective tissue diseases, and certain malignancies are concerning as long-term complications, especially in immunocompromised individuals [9].

Laboratory and Imaging

The diagnosis of IM depends on presence of the typical symptoms and a positive heterophile "monospot" antibody test. When positive in the presence of IM symptoms, the heterophile test has an approximate sensitivity of 85% and specificity of 94% [6]. However, the heterophile tests have several limitations. Nearly 10% of patients with IM are consistently heterophile-negative [8]. Furthermore, the test may be falsely negative in approximately 40% of children 4 years of age or younger who do not develop heterophile antibodies following primary EBV infection. Other infections like toxoplasmosis and cytomegalovirus (CMV), certain malignancies, and autoimmune diseases have also been linked with positive heterophile antibody tests. Finally, heterophile antibodies can persist for a year or more and therefore are not always diagnostic of an acute EBV infection [14].

If the heterophile test is negative, a complete blood count (CBC) with differential can be done. A finding of marked lymphocytosis (over 50% of all lymphocytes) with atypical cells comprising at least 10% of all leukocytes would suggest heterophile-negative EBV-induced IM according to the Hoagland criteria [9].

Chronic EBV infection can be characterized by the antibody profile of negative viral capsid antigen (VCA) IgM indices, very high VCA IgG indices, and modestly elevated Epstein-Barr virus nuclear antigen (EBNA) -1 IgG levels [14].

Special Testing

If EBV is strongly suspected but heterophile antibody testing is negative, EBV-specific antibodies VCA IgM, VCA IgG, and EBNA-1 IgG can be obtained for confirmation of infection [14]. Other modalities such as immunoblotting and serial quantitative measurements of EBV DNA in the blood can also be considered.

Differential Diagnosis

Table 1 includes the differentials diagnosis of IM [9]. Diagnostic testing is particularly important if the patient is pregnant since conditions such as CMV, human immunodeficiency virus (HIV), and toxoplasma infections can cause infection and negative fetal outcomes.

Treatment

Behavioral

Parents can be advised against kissing children on the mouth to limit oral shedding of the virus and to keep toys, particularly in daycare spaces, clean to prevent transmission. Physical activity of any intensity within the first 3 weeks of illness may increase risk of splenic rupture and therefore should be restricted [13].

Medications\Immunizations and Chemoprophylaxis

Treatment is generally supportive for IM. Glucocorticoids can decrease the severity of sore throat associated with IM within the first 12 h of treatment, but neither these medications nor antivirals

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Table 1 Differential diagnosis for infectious mononucleosis

Diagnosis	Distinguishing features
Streptococcal pharyngitis	Abrupt onset of sore throat during peak incidence (winter and early spring) months Exudative pharyngitis, absence of splenomegaly or hepatomegaly Positive rapid strep or throat culture
CMV	Contact with children, especially younger than 2 years of age Anicteric hepatitis Usually heterophile antibody negative
Toxoplasmosis	History of ingesting undercooked meat, exposure to cats or cat droppings Nontender lymphadenopathy Usually heterophile antibody negative
HIV/Acquired Immuno-Deficiency Syndrome (AIDS)	Intravenous drug use, unprotected sexual intercourse, or other HIV exposure risks Mucocutaneous lesions, rash, diarrhea, weight loss, nontender lymphadenopathy Adults with HIV/AIDS are more likely to have a concurrent infection from EBV
Adenovirus	Nonspecific upper respiratory symptoms including cough Less systemic lymphadenopathy Heterophile antibody negative
Leukemia	CBC abnormalities including very high or low white blood cell count, low hemoglobin with signs of hemolysis, and low platelets
Drug side-effect	Minocycline, carbamazepine, phenytoin, isoniazid

such as acyclovir have been shown in studies to decrease the severity or length of illness of IM [13].

Three prophylactic EBV vaccine candidates have been tested in humans [14]. Two were based on the major surface glycoprotein gp350 of EBV that allows the virus to attach to human B-lymphocytes and cause infection. The third prophylactic EBV vaccine candidate was an adjuvant EBNA-3A peptide designed to control expansion of EBV-infected B cells by general CD8 T-cell immunity to EBNAs. At this time, the clinical application of vaccines is limited to prevention of complications associated with EBV rather than reducing rates of primary EBV infection [16].

Referrals

In cases of airway obstruction, an otolaryngology consultation may be urgently warranted. Referrals to other specialists may be necessary depending on complications.

Counseling

Majority of the patients with EBV infection recover without sequelae and develop lifelong immunity to controlling the latent virus [17]. IM is mostly self-limiting and recovery is common in 2–4 weeks.

Patient Education and Activation

Measures such as frequent handwashing and limiting shared items, such as toothbrushes and eating utensils, can help maintain good hygiene in general. Patients should be advised to maintain adequate hydration, rest, and good nutrition. They should also be educated on potential complications and the course of the illness, and given clear instructions for follow-up and return to physical activity [17].

Prevention

Due to the very high worldwide prevalence of EBV antibodies in adults, it is nearly impossible to avoid exposure to EBV. The role of antivirals (e.g., acyclovir, valacyclovir, ganciclovir, and

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valganciclovir) in prevention of posttransplant EBV disease is uncertain [14].

Family and Community Issues

Further investigation into asymptomatic primary infection in adolescents and young adults is warranted.

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Viral Infections of the Respiratory Tract

41

Lee Coghill and Alfred C. Gitu

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Definition/Background

Respiratory viruses are ubiquitous organisms that can cause a wide spectrum of clinical manifestations in patients of all ages ranging from mild or even asymptomatic upper respiratory tract infections to fatal illnesses with multiorgan failure [1]. Viral infections of the respiratory tract are also common in all age groups and are the leading cause of mortality in children under 5 years of age in developing countries [2]. They pose a significant symptom burden for individuals and a high financial burden to society – mostly due to loss of productivity, healthcare costs, and school absenteeism [3]. Advances in diagnostic testing and improved ability to detect pathogens have demonstrated that viral pathogens are important causal pathogens of respiratory tract infection even in immunocompetent patients. As the number of elderly adults and those with chronic medical conditions increases, the burden of viral respiratory infections has also increased [4].

Additionally, viral respiratory infections play an important role as a trigger for exacerbations of chronic respiratory diseases, such as asthma, or chronic obstructive pulmonary disease (COPD) [3].

Epidemiology

In the United States, 25 million people visit their family doctors every year with uncomplicated upper respiratory infections [1]. The epidemiology of respiratory tract infection is changing due in part to the aging of the US population and the success of childhood vaccination programs [4].

The incidence and impact of these viral infections tend to be greatest at the extremes of life: in infancy and in the elderly. Up to 70% of children and 30% of adults with respiratory viral infection may develop lower respiratory symptoms. The virus is often the sole pathogen identified [5]. In addition, respiratory viruses frequently initiate a cascade of events that ultimately leads to bacterial infection [1]. Most respiratory virus infections occur in the fall and winter months, but viruses such as human adenovirus, and potentially SARS-COV-2, do not show a seasonal variation in spread [6].

Etiology

Some of the more common viral causes of respiratory tract infection include human adenovirus, influenza virus types A and B, human metapneumovirus, parainfluenza virus, respiratory

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syncytial virus(RSV), rhinovirus (most common), and coronavirus [7, 8]. All of them are RNA viruses, except for adenovirus, which is a DNA virus.

Transmission

Respiratory viruses are readily transmitted from person-to-person through direct contact with infected persons and aerosolization of infective droplets during coughing and sneezing or, indirectly, by hand transfer of contaminated secretions or transfer from contaminated objects or surfaces to the nasal or conjunctival epithelium of susceptible persons (see Table 1) [9, 10].

Pathogenesis

The pathogenesis of viral respiratory tract infections is not fully understood but appears to involve a delicate balance between virus infection and clearance by the host. Inoculation occurs through the upper respiratory tract, primarily the eyes and nose, and most viruses multiply locally in the respiratory epithelium of the large and small airways without causing systemic infection. Depending on the virus, this may result in inflammation, increased mucosal secretions, and leukocyte infiltration as well as changes in ciliary and mucus-producing functions. Both upper and lower ciliated airway cells can be destroyed and the epithelium denuded, with clearance mechanisms and phagocytic cell function compromised. This damage creates susceptibility to superinfection by bacteria. Host immune responses also appear to play an important role in pathogenesis. For example, certain viruses appear to interact with the immune system in ways that trigger immediate hypersensitivity reactions, which may lead to virus-induced wheezing and asthma.

A variety of responses involving interferon and cytotoxic T-cell responses with release of cytokines and chemokines are associated with elimination of the virus and subsequent recovery. Various degrees of cytokine release occur, with the most severe of these representing the entity known as a "cytokine storm" [9].

Laboratory Testing

Most respiratory viral infections are diagnosed clinically [11]. Testing may also be indicated for certain viral infections when management decisions or infection control will be impacted by the result (e.g., influenza and COVID-19).

Table 1 Common routes of transmission for respiratory viruses. Adapted from [10]. Used with permission

Transmission route	Particles involved and particle characteristics	Characteristics/definition of transmission
Contact		Self-inoculation of mucous membranes by contaminated hands
Direct	Deposited on persons	Virus transfer from one infected person to another
Indirect	Deposited on objects	Virus transfer through contaminated intermediate objects (fomites)
Airborne		
Droplet	Droplets (>5 μm) Remain only briefly in air (<17 min) Dispersed over short distances (<1 m)	Short-range transmission Direct inoculation of naïve person through coughing/sneezing/breathing of infected person Deposition mainly on mucous membranes and upper respiratory tract
Aerosol	Aerosols, droplet nuclei (<5 μm) Remain in air for prolonged periods Dispersed over long distances (>1 m)	Long-range transmission Inhalation of aerosols in respirable size range Deposition along the respiratory tract, including the lower airways

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Nasopharyngeal specimens are often used in routine clinical practice and in many surveillance studies [12].

Testing Methods [9]

- Viral cultures
  - Highly specific but with low sensitivity
  - Labor, resource, and time intensive
- Direct antigen detection tests
  - Immunofluorescence or immunoassay
  - Moderate specificity and sensitivity
  - Rapid and amenable to point-of-care testing
- Nucleic amplification tests
  - Polymerase chain reaction (PCR) and other nucleic acid amplification assays
  - Highly sensitive and specific
  - The new reference standard in respiratory virus testing
- Serology
  - Generally not helpful in the acute clinical setting
  - Often used in research and epidemiological studies
- Multiplex testing platforms
  - Testing for multiple respiratory pathogens from a single specimen
  - Becoming more routinely used in hospitals and emergency rooms

Common Cold

Definition/Background

The common cold is a conventional term for a mild upper respiratory illness, the hallmark symptoms of which are nasal stuffiness and discharge, sneezing, sore throat, and cough [13].

Common colds are defined as upper respiratory tract infections that affect predominantly the nasal part of the respiratory mucosa. Because upper respiratory tract infections can affect any part of the mucosa, it is often arbitrary whether an upper respiratory tract infection is called a "cold" or "sore throat" ("pharyngitis" or "tonsillitis"), "sinusitis," "acute otitis media," or "bronchitis." Sometimes all areas (simultaneously or at different times) are affected during the same illness [14].

Although the term tends to imply that there is a single cause for the illness, the common cold is actually a heterogeneous group of diseases caused by numerous viruses that belong to several different families [13].

Etiology/Spread

The viral causes of the common cold are rhinoviruses (30–50%), coronaviruses (10–15%), influenza viruses (5–15%), RSV (5%), and adenoviruses, enteroviruses, and human metapneumovirus (all <5%) [13]. For many colds, no infecting organism can be identified [14].

Transmission of common cold infections is primarily through direct contact rather than droplet spread [14].

Prognosis

Common colds are usually short lived, lasting a few days, with a few lingering symptoms lasting longer. Symptoms peak within 1–3 days and generally clear by 1 week, although cough often persists. Although they cause no mortality or serious morbidity, common colds are responsible for considerable discomfort, lost work, and medical costs.

Epidemiology

The occurrence of the common cold shows clear seasonality. In temperate regions of the world, the frequency of respiratory infections increases rapidly and remains high in the winter months, decreasing as the weather warms again in spring. In tropical areas, most colds arise during the rainy season. The incidence of upper respiratory infections is inversely proportional to age. On average, young children have 6–8 and adults 2–4 colds per year. During the first years of life, boys seem to

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have more respiratory infections than girls, but this difference is reversed later in life. Day-care attendance is a major risk factor for respiratory illnesses in children, and the frequency of colds increases with the number of children in the group. However, frequent infections in the preschool years may lower the frequency of the common cold during school years. Psychological stress is associated with susceptibility to the common cold in a dose-dependent manner. Finally, some reports indicate that heavy physical training increases the risk of respiratory infections, whereas moderate physical activity may decrease risk [13].

Clinical Manifestations

Rhinovirus infections typically start with a sore throat, which is soon accompanied by nasal stuffiness and discharge, sneezing, and cough. The soreness of the throat usually resolves quickly, while the initial watery rhinorrhea turns thicker and more purulent. The purulence of the nasal discharge is generally not associated with changes in the nasopharyngeal bacterial flora and is not thought to indicate a simultaneous bacterial infection of the nasal mucosa. Fever is an infrequent finding during rhinovirus infections in adults, but it is fairly common in children with upper respiratory infections of any cause. Other symptoms associated with the cold syndrome include hoarseness, headache, malaise, and lethargy. Myalgia is an occasional complaint in patients with colds, although it is a more typical feature of influenza infection.

Diagnosis

Diagnosis is made clinically and testing is rarely necessary.

Treatment

Because the symptoms of the common cold are universally self-limited, treatment is aimed at reducing the duration and severity of illness. Informing patients about the natural course of the common cold can help manage expectations, limit antibiotic use, and avoid unnecessary over-the-counter purchases [15]. Antibiotics have no role in the treatment of acute viral upper respiratory infections in children or adults and should not be prescribed [16, 17].

Treatments with proven effectiveness, and those proven to be ineffective or even harmful, are listed in Table 2.

The Food and Drug Administration has issued an advisory that over-the-counter cold medications containing a decongestant or antihistamine should not be used to treat children younger than 4 years because of lack of benefit and low but

Table 2 Treatments for the common cold [14, 15]

Adults		Children	
Effective	**Ineffective**	**Effective**	**Ineffective**
OTC NSAIDs	Antihistamine monotherapy	Intranasal ipratropium	Antibiotics
Zinc	Increased fluid intake	Analgesics	Antihistamines
Nasal decongestants	Codeine	Honey	Antitussives
Intranasal ipratropium	Echinacea	Acetylcysteine	Echinacea
	Intranasal corticosteroids	Nasal saline irrigation	Intranasal corticosteroids
	Pelargonium sidoides (African geranium)	Ointment containing camphor, menthol, and eucalyptus oils	
	Steam	Vitamin C – initiated prior to the onset of symptoms	
	Vitamin C, D, or E		

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significant mortality rates associated with their use in this population [18, 19]. The only safe and effective treatments for children are analgesics, acetylcysteine, honey (for children older than 12 months of age), nasal saline irrigation, intranasal ipratropium, and menthol rub [15].

Complications [13]

Although the common cold is usually a self-limited illness of short duration, the viral infection is sometimes accompanied by a bacterial complication. In children, the most common bacterial complication is acute otitis media, which occurs in about 20% of children with viral upper respiratory infections. Other common bacterial complications of viral upper respiratory infections include sinusitis and pneumonia. Sinusitis has been estimated to occur as a complication in 0.5–2% of colds. Pneumonia associated with a viral upper respiratory infection is often a bacterial complication of the predisposing viral illness, but it can also be an extension of the viral illness to the lung.

Acute viral respiratory infections are also associated with acute exacerbations of asthma and COPD. In immunocompromised patients, RSV is usually the most common cause of severe viral respiratory illness, but rhinovirus infections have also been associated with severe and even fatal lower respiratory tract disease.

Laryngitis

Definition/Background

Laryngitis is defined as inflammation of the larynx which can be infectious or non-infectious. Acute laryngitis usually lasts less than 3–4 weeks and is most commonly caused by the same viruses as the common cold described earlier in this chapter.

Approach to the Patient

Symptoms of laryngitis typically include dysphonia (hoarseness of voice or change in voice pitch) and/or pain in the anterior neck typically coinciding with other symptoms of an upper respiratory infection. Acutely, it is important to differentiate between other possible causes of laryngitis such as bacterial or fungal infection, allergic rhinitis, acid reflux, voice misuse and overuse, toxic inhalation or ingestion, postnasal drainage, or trauma [20].

Treatment

There are no clinical criteria that help to distinguish clearly between viral and bacterial causes of laryngitis. The routine use of antibiotics in acute laryngitis does not improve clinical outcomes, however [21]. Treatment is typically supportive including voice rest, avoidance of irritants, humidification, local lubrication, and systemic hydration. Despite widespread use, corticosteroids are not routinely recommended in patients with hoarseness, except in children with croup [22]. Direct visualization of the vocal cords by laryngoscopy should be considered for symptoms lasting >3 weeks or for patients with stridor, recent surgery, recent intubation, radiation therapy to the neck, or weight loss.

Influenza

Definition/Background

Influenza is an acute respiratory illness caused by the influenza virus which is a single stranded RNA virus from the *Orthomyxoviridae* family. Human influenza virus subtypes A and B cause the epidemics of human disease, while influenza virus type C causes a mild respiratory illness similar to the common cold. Influenza viruses have genetic properties that can create "antigenic shifts" which have the potential to cause pandemics of human illness due to lack of preexisting immunity [23]. In temperate climates, seasonal epidemics occur annually in the winter months (see Fig. 1), while in tropical climates influenza cases occur intermittently throughout the year. Worldwide, it is estimated that influenza causes 290,000–650,000 deaths each year [24].

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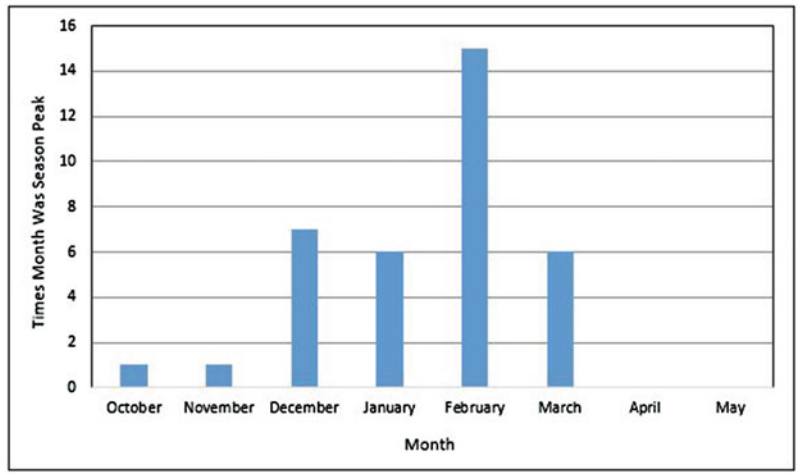


Fig. 1 Peak month of flu activity in the United States: 1982–1983 through 2017–2018 [25]

Clinical Manifestations

Infection of the respiratory tract by influenza virus commonly causes fever, cough, sore throat, nasal congestion or rhinorrhea, headache, muscle aches (myalgias), and malaise. Diarrhea and/or vomiting may be present, especially in children. Complicated infection can lead to lower respiratory tract disease, central nervous system involvement (e.g., encephalopathy, encephalitis), severe dehydration, or secondary complications such as organ failure and septic shock [26]. Symptoms typically begin abruptly after a 1–4-day incubation period and typically last about 3–7 days, but cough and fatigue may persist beyond 2 weeks [27]. Influenza infection can also exacerbate other underlying chronic diseases such as asthma, COPD, and congestive heart failure.

Treatment

Treatment for influenza infection is largely supportive, and the same principles typically apply to the common cold as described previously in this chapter. Antivirals can reduce symptom duration by 0.5–1 day in an average adult, but may reduce mortality, especially in high-risk patients (severe illness, patients <2 years old or >65 years old, patients who are pregnant, residents of long-term care facilities, patients with other chronic medical conditions or immunosuppression). The greatest benefit for antiviral treatment has been demonstrated when given as soon as possible, especially in the first 48 h after symptom onset. Treatment with antivirals is recommended for up to 5 days after the onset of illness in hospitalized patients to reduce morbidity and mortality. There are currently three different classes of antiviral medications: neuraminidase inhibitors, cap-dependent endonuclease inhibitors, and adamantanes (see Table 3). Currently the neuraminidase inhibitors and the novel cap-dependent endonuclease inhibitors are active against circulating influenza A and B strains and are approved by the Food and Drug Administration (FDA). The adamantanes are not recommended for treatment because they are only active against influenza A and there are currently very high rates of resistance among circulating influenza A strains [28].

Prevention

In addition to basic infection mitigation measures for infections of the respiratory tract (discussed later), vaccination is a major strategy for prevention and control of influenza. Vaccine composition is adjusted each year based on the predicted strains for the upcoming flu season and is coordinated by the World Health Organization. Current recommendations call for annual vaccinations in all patients 6 months of age and older with any of the licensed, age-appropriate vaccines including the inactivated influenza vaccine, recombinant

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Table 3 Drugs available for the treatment of influenza in the United States [28]

Drug name	Method	Age	Mechanism of action	Activity against influenza strains	FDA approval	Notes
Oseltamivir phosphate (Tamiflu)	Pill or liquid suspension	>14 days	Neuraminidase inhibitor	A and B	Yes	Early treatment of hospitalized patients has been reported to reduce morbidity and mortality in children and adults
Zanamivir (Relenza)	Inhaled	>7 years	Neuraminidase inhibitor	A and B	Yes	Contraindicated in patients with asthma or COPD
Peramivir (Rapivab)	Intravenous	>2 years	Neuraminidase inhibitor	A and B	Yes	
Baloxavir marboxil (Xofluza)	Pill	>12 years	Cap-dependent endonuclease inhibitor	A and B	Yes	Not recommended in pregnancy, breastfeeding, complicated illness, or hospitalized patients due to lack of data
Amantadine	Pill	Not recommended	Adamantane	A only	No	High levels of resistance to adamantanes among currently circulating influenza A viruses
Rimantadine	Pill	Not recommended	Adamantane	A only	No	High levels of resistance to adamantanes among currently circulating influenza A viruses

influenza vaccine, or live attenuated influenza vaccine [29]. The number needed to vaccinate in order to prevent a case of influenza varies according to the "match" between the vaccine and circulating virus strains. Fewer than 1% of vaccine recipients experience fever after vaccination, and other risks of harm are much lower [30]. Overall there is significant benefit for vaccination compared to potential harm, and while yearly efficacy can fluctuate, universal vaccination is strongly encouraged to improve herd immunity to influenza, thus protecting high-risk individuals.

Antivirals are not generally recommended for chemoprophylaxis due to increasing antiviral resistance, and annual influenza vaccination is the preferred method of prevention. Oseltamivir and zanamivir can be considered for chemoprophylaxis for prevention in patients with severe immune deficiencies or who are at high risk of influenza complications who have been exposed to a person with influenza in the first 2 weeks following vaccination or who cannot receive influenza vaccination due to a contraindication [28].

Acute Bronchitis

Definition/Background

Acute bronchitis is a self-limited infection of the epithelial cells of the bronchi characterized by the presence of cough, with or without sputum

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production. The majority (>90%) of cases of uncomplicated acute bronchitis are due to a viral infection, most commonly influenza A and B, parainfluenza, RSV, coronavirus, adenovirus, rhinovirus, and human metapneumovirus. A minority of cases may be caused by non-viral organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Bordetella pertussis*, *Legionella*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*. Acute bronchitis can also be caused by inhalation of irritants such as cigarette smoke, ammonia, and other noxious substances. Acute bronchitis is one of the most common diagnoses encountered by family physicians with approximately 100 million office visits per year. This number is equivalent to about 10% of outpatient visits in the United States [31].

Approach to the Patient

The symptoms of acute bronchitis overlap with other clinical syndromes of upper and lower respiratory tract infections and typically include cough for at least 5 days (with or without sputum production), dyspnea, low-grade fever, headache, wheezing, rhonchi, or other signs of obstruction. Symptoms generally last for 2–3 weeks, but the cough may persist for up to 8 weeks in some cases [32]. Despite widespread belief that purulent sputum indicates bacterial infection, sputum color does not appear to be predictive of bacterial infection in patients with acute cough with otherwise healthy lungs [33]. In the absence of abnormal vital signs, history, or physical exam findings that may be consistent with pneumonia, a chest radiograph is not necessary in most cases.

Treatment

As in other upper respiratory infections, treatment is generally targeted toward symptoms and balanced against risks of side effects. Routine use of antibiotics is not recommended for uncomplicated acute bronchitis as they have limited efficacy and significant adverse effects [34]. Inhaled albuterol can be useful in patients with asthma or COPD but may not reduce cough in children or adults without underlying lung disease [35].

Coronavirus Infections

Human Coronavirus Types [7]

Coronaviruses are RNA viruses named for the crown-like spikes on their surface.

Common human coronaviruses (causing mild respiratory infections)

1. Alpha coronaviruses
   a. 229E
   b. NL63
2. Beta coronavirus
   a. OC43
   b. HKU1

Other Human Coronaviruses (Causing More Severe Respiratory Disease)

3. MERS-CoV (the beta coronavirus that causes Middle East respiratory syndrome or MERS)
4. SARS-CoV-1 (the beta coronavirus that causes severe acute respiratory syndrome or SARS)
5. SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019 or COVID-19)

COVID-19

Definition/Background

After the first reported cases in Wuhan province, China, in December 2019, COVID-19 has become a global pandemic with over ten million confirmed cases and over 500,000 deaths by the end of June 2020 [36].

Clinical Presentation

Patients infected with SARS-CoV-2 may remain asymptomatic or develop mild, moderate, or severe illness. Mild symptoms include cough, fever, malaise, gastrointestinal symptoms, and anosmia [37]. Severe illness usually begins approximately 1 week after the onset of symptoms. Dyspnea is the most common initial

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symptom of severe disease and is often accompanied by hypoxemia [38]. Patients with mild disease usually recover at home, while those with moderate or severe symptoms require hospitalization for observation and supportive care [38]. Hypercoagulability also seems to be an important pathophysiological mechanism that may lead to damage in a number of end organs.

There are few proven therapies for COVID-19, but various agents and techniques are under investigation as of this writing. Infection control and prevention efforts center on personal protective equipment for healthcare workers, universal masking, social distancing, vaccination, as well as testing and tracing [37].

The median incubation period, from exposure to symptom onset, is approximately 4–5 days, and 97.5% of patients who are symptomatic will have symptoms within 11.5 days after infection.

Risk factors for complications of COVID-19 include older age (e.g., >65 years), cardiovascular disease, chronic lung disease, hypertension, diabetes, and obesity.

New and Emergent Respiratory Infections [39]

Besides COVID-19, other respiratory diseases caused by viral agents have included severe acute respiratory syndrome virus (SARS), Middle East respiratory syndrome virus (MERS), and pandemic influenza caused by a novel H1N1 strain [39].

Common themes in emerging infections include zoonotic hosts and changes in human behavior, including increased international travel and/or modification of the physical environment [39].

SARS

Etiology, Epidemiology, and Clinical Presentation

Severe acute respiratory virus (SARS) is a rapidly fatal pulmonary infection caused by the SARS coronavirus (SARS-CoV). The first documented outbreak occurred primarily in China from 2002 to 2004 with regional outbreaks in North America and Europe attributed to human-to-human transmission from infected international travelers. A total of 8096 cases from 29 countries, including 774 fatalities, were identified during the course of the outbreak (case fatality rate: 9.6%) [39]. There have not been any known cases of SARS reported worldwide since 2004.

MERS

Etiology, Epidemiology, and Clinical Presentation

Middle East respiratory syndrome (MERS) was first identified during September 2012 in a Saudi Arabian patient with respiratory failure. In comparison to the rapid spread and subsequent quiescence of SARS-CoV, MERS-CoV has continued to circulate and produce sporadic outbreaks both within the Arabian Peninsula and in countries where infected patients have traveled. There have been 2266 confirmed cases of MERS and 804 fatalities (case fatality: 35.5%).

The clinical presentation varies from asymptomatic infection to severe disease with respiratory failure. In general, older patients and those with chronic comorbid conditions (diabetes, heart disease) are at greatest risk for progression to respiratory failure.

Pandemic Influenza 2009

Etiology, Epidemiology, and Clinical Presentation

In contrast to the emergence of COVID-19, MERS, and SARS, the 2009 H1N1 influenza pandemic was a re-emergence of a pathogen most commonly responsible for seasonal infections, but with demonstrated pandemic potential. The virus (H1N1pdm09) first emerged in Mexico during the spring of 2009. The virus contains gene segments from human, porcine, and avian influenza strains. Since its introduction in human populations, the 2009 strain has become a commonly circulating strain and is now routinely incorporated into the seasonal vaccine.

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The full clinical spectrum of pandemic influenza infection differs little from seasonal influenza. However, during the 2009 pandemic, patients infected with the pandemic strain were younger, were less likely to have underlying conditions, more frequently required ventilatory support or ICU care, and had relatively frequent extrapulmonary complications. In those cases progressing to severe disease, acute onset hypoxemia and acute respiratory distress were frequent. In addition, patients with severe influenza requiring hospitalization were at increased risk of developing secondary bacterial pneumonia, acute kidney injury, and requirements for mechanical ventilation.

Prevention

Respiratory viral infections are predominantly transmitted through infected droplets. Following general hygienic practices helps to decrease transmission. These include regular hand hygiene, minimizing contact with sick individuals, and avoiding the sharing of personal items. Following "cough etiquette," including covering the nose and mouth with a tissue while coughing, proper disposal of tissue, and prompt hand washing, is also shown to decrease spread of respiratory infections [40]. Currently, an effective vaccine is available only for influenza. Other measures of prevention include antivirals for high-risk patients exposed to influenza and use of palivizumab, a monoclonal antibody, in high-risk individuals to prevent respiratory syncytial virus (RSV) infections. New evidence has been growing to support universal mask-wearing and physical distancing and avoidance of large social gatherings during times of high levels of community viral transmission such as an epidemic or pandemic. During times of critical supply shortages, higher levels of personal protective equipment including gowns, gloves, surgical masks, and respirators should be reserved for healthcare workers and other medical first responders. The general public (with the exception of children under the age of 2, anyone who has trouble breathing, or anyone is unable to remove a mask without assistance) should use cloth face coverings to help reduce the spread of disease from symptomatic and asymptomatic carriers [41].

Family and Community Issues

Antibiotic resistance in the healthcare setting is a growing threat to public health, and, as of 2019, 2.8 million people become infected and 35,000 people die each year from antibiotic-resistant infections [42]. In part, antibiotic-resistant infections stem from the prescribing of antibiotics when they are not needed, as in the case of viral respiratory tract infections.

Many strategies can help to reduce inappropriate antibiotic use including patient information handouts, use of procalcitonin levels, point-of-care C-reactive protein testing, print-based or computer decision support strategies, delayed antibiotic prescription, the use of diagnostic labels that reinforce the benign nature of the condition (e.g., "chest cold"), and helping to reframe patient expectations relating to length of illness [43]. Ultimately, good physician-patient communication and patient education can help combat this growing threat to public health. By acknowledging the suffering and discomfort caused by viral infections, the family physician is able to partner with the patient, proactively treat their symptoms, and offer them support without exposing them to further risk through inappropriate antibiotic use.

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Sinusitis, Tonsillitis, and Pharyngitis

42

Laeth S. Nasir and Alexander Tu

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Sinusitis

Sinusitis is defined by inflammation of the mucosa of the paranasal sinuses. In addition to the sinuses, the inflammation almost always involves the nasal cavity, and thus the term *rhinosinusitis* is often used interchangeably with *sinusitis* [1]. For the remainder of this chapter, the term *rhinosinusitis* will be used. Rhinosinusitis is further separated into three classifications based on duration and recurrence of symptoms [2].

Acute rhinosinusitis: signs and symptoms lasting less than 4 weeks

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Recurrent acute rhinosinusitis: four episodes lasting less than 4 weeks with complete resolution of symptoms in between episodes

Subacute rhinosinusitis: signs and symptoms lasting 4–12 weeks

Chronic rhinosinusitis: signs and symptoms lasting 12 weeks or longer

Epidemiology

Rhinosinusitis is an extremely common condition, with about one out of eight adults being diagnosed in the United States each year, resulting in nearly 30 million diagnoses [3]. Women are more frequently affected by rhinosinusitis than men, and adults older than 45 years old are at higher risk [3]. Southern regions of the United States are also disproportionately affected compared to other regions such as the Northeast and West [3]. Chronic rhinosinusitis has an enormous economic burden: direct costs for chronic rhinosinusitis management have been estimated at around $13 billion per year in the United States, while indirect costs related to chronic sinusitis-related loss in work productivity have been estimated to be over $20 billion per year [4].

Risk Factors

Rhinosinusitis is more common in individuals with allergic rhinitis and/or asthma [5]. Other risk factors include anatomic abnormalities such as polyps or a deviated septum, in addition to systemic conditions such as cystic fibrosis or other conditions associated with immunodeficiencies [6]. Other risk factors include air travel and smoking or exposure to second-hand smoke.

Microbiology

The most common causes of acute rhinosinusitis are viral in etiology. Common pathogens include rhinovirus, influenza, and parainfluenza virus species. Secondary bacterial infection is uncommon. It is estimated that only 0.5–2% of cases progress to acute bacterial rhinosinusitis [7]. Common bacterial causes of rhinosinusitis include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* [7]. Rarely, fungal infection can lead to acute rhinosinusitis; these cases occur almost exclusively in immunosuppressed individuals, such as people living with HIV, patients undergoing chemotherapy, or those with uncontrolled diabetes mellitus.

Clinical Presentation

Rhinosinusitis classically presents with flu-like symptoms, including nasal congestion, mucopurulent nasal discharge, headache, and facial or sinus pain and/or pressure that worsens when bending forward [8]. Other symptoms might include fever, cough, dental pain, hyposmia or anosmia, and ear pressure or fullness.

Both acute viral rhinosinusitis and acute bacterial rhinosinusitis present similarly, and there are no reliable clinical criteria that distinguish between etiologies reliably [7]. However, acute viral rhinosinusitis and acute bacterial rhinosinusitis tend to have different clinical courses:

In acute viral rhinosinusitis, symptoms typically peak in severity between days 3 and 6, and either symptomatically improve or completely resolve within 7–10 days [2]. Fever, if present, will generally present and resolve within the first 24–48 h of the illness, after which respiratory symptoms become more prominent [7]. Viral rhinosinusitis can present with purulent discharge, which is generally a sign of nasal/sinus mucosa inflammation. Typically, nasal discharge initially presents clear, becomes purulent, then becomes clear again.

In acute bacterial rhinosinusitis, symptoms tend to last longer than 10 days [2, 7]. Often, there is a biphasic pattern of illness ("double worsening"), in which there are worsening symptoms after an initial period of improvement. However, individual symptoms cannot be accurately used to distinguish between bacterial or viral rhinosinusitis. Rather, the full clinical picture

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and temporal pattern must be considered altogether when making a formal diagnosis [2].

Diagnosis

The diagnosis of rhinosinusitis is based on clinical signs and symptoms. Per guidelines from the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), acute rhinosinusitis can be diagnosed when patients present with: less than 4 weeks of purulent nasal discharge **and** severe nasal obstruction, facial pain/pressure/fullness, or both [7]. The clinical diagnosis of acute bacterial rhinosinusitis is made when symptoms persist for more than 10 days without improvement, or with worsening of symptoms within 10 days after initial improvement ("double worsening").

Patients with acute bacterial rhinosinusitis associated with signs or symptoms suggestive of ophthalmologic, neurologic, or surrounding soft tissue involvement are diagnosed as having **complicated acute bacterial rhinosinusitis** and require urgent evaluation and treatment. Concerning signs and symptoms include:

- Periorbital edema or erythema
- Vision changes (double vision, blurry vision)
- Proptosis
- Altered mental status
- Meningeal signs (neck stiffness, Kernig's and Brudzinski's sign)
- Pain with eye movement

Physical Exam

Physical exam findings may include warmth and/or tenderness over the cheekbones, and clear or purulent discharge within the nose or posterior pharynx [2]. Facial pain or pressure with percussion of the sinuses may also be present, though the sensitivity and specificity of these findings have not been established and are not diagnostic alone [9]. Anterior rhinoscopy may also show nasal mucosa erythema and edema, narrowing of the middle meatus, turbinate hypertrophy, and nasal discharge.

Diagnostic Imaging and Laboratory Studies

Rhinosinusitis is typically a clinical diagnosis, though imaging may be useful in particular settings. If there is suspected intraorbital or intracranial complications, immunocompromised states, or severe and/or recurrent disease, computed tomography (CT) scan of the head and paranasal sinuses with contrast should be considered [10] and may also be used to exclude a diagnosis of rhinosinusitis. However, CT findings may not correlate with overall severity of symptoms. Plain radiographs are **not** useful due to their poor sensitivity and specificity [11]. Nasal endoscopy can be used for better visualization of nasal purulence than an anterior nasal exam. However, it is not essential for diagnosis and is often impractical in the primary care setting [12]. Microbiological testing of sinus aspirates or endoscopic cultures can be collected to distinguish between infectious etiologies, but these are seldom used outside of tertiary settings [12].

Treatment

Initial Management

Acute viral rhinosinusitis should be treated symptomatically, including the use of analgesics, antipyretics, topical intranasal glucocorticoids, hydration, and nasal irrigation with saline [8]. Over-the-counter analgesics and antipyretics such as nonsteroidal anti-inflammatory drugs and acetaminophen are usually sufficient for pain and fever relief [2, 7].

Topical intranasal glucocorticoids have been shown to significantly improve pain and nasal congestion when compared to placebo [13]. Higher doses of intranasal glucocorticoid are more effective in reducing symptoms without serious adverse effects [13]. Minor adverse events may include epistaxis, nasal itching, and headache. While the adjunctive use of oral glucocorticoids can provide slight improvements in symptoms for patients who are prescribed antibiotics [14], the side effects and risks of systemic glucocorticoid use make it a less preferred option

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for patients diagnosed with acute bacterial sinusitis [8] or chronic rhinosinusitis with or without nasal polyps [15].

Nasal saline irrigation may provide some symptomatic relief such as reduced nasal secretion and obstruction, as well as reduced use of decongestant medication, though the evidence is not extremely robust [16]. However, it is a relatively safe therapy (provided the irrigants are sterile or bottled water) with minor adverse effects, such as nasal burning and irritation [16]. It should also be borne in mind that those needing to limit their sodium intake may not be able to use this method.

Oral decongestants have not been shown to be efficacious at reducing symptoms of rhinosinusitis [2] and are commonly associated with adverse effects (nervousness, irritability, headache, nausea). Intranasal decongestants may improve nasal congestive symptoms in some patients [2] but should be used cautiously and for no more than three consecutive days to avoid rebound congestion [17].

Antihistamines can provide symptomatic relief due to its drying effects, particularly for patients with underlying allergic rhinitis [18]. However, there is no evidence for significant efficacy in acute rhinosinusitis [2]. In addition, antihistamines, particularly the first-generation formulations, have been associated with adverse effects such as anticholinergic effects (e.g., dry mouth and eyes, constipation, blurred vision, drowsiness) and should be avoided in certain populations such as the elderly [7].

Mucolytics thin mucus and may improve nasal drainage. However, there is no evidence to support their use in rhinosinusitis [2].

Antimicrobial Therapy

The decision to use antibiotic therapy should be based on a shared consensus between the physician and the patient once a diagnosis of bacterial rhinosinusitis has been made. Antibiotic therapy has been shown to have significant clinical improvement at 7–16 days compared to placebo, but the difference is small [19]. Thus, the potential benefits of antibiotic therapy must be considered against potential adverse effects, including allergic reactions and development of drug-resistant bacteria.

Empiric treatment of acute bacterial rhinosinusitis in patients without a penicillin allergy is most often amoxicillin-clavulanate at a dose of 875 mg of amoxicillin and 125 mg of clavulanate orally two times daily for 5–10 days [2, 7]. The addition of clavulanate improves coverage for resistant strains of *Haemophilus influenzae* and *Moraxella catarrhalis.* For patients allergic to penicillin, the options include doxycycline (100 mg orally twice a day or 200 mg daily for 5–10 days), clindamycin (300 mg orally three times a day for 10 days), cefexime (400 mg orally once a day for 10 days), levofloxacin (500 mg orally once a day for 5–10 days), or moxifloxacin (400 mg orally once a day for 5–10 days) [2, 7].

Patients who have failed initial antibiotic treatment should be started on a different antibiotic than their initial therapy.

It is important to note that the Food and Drug Administration has advised that the use of fluoroquinolones (levofloxacin, moxifloxacin) be considered after other alternatives have been considered due to their potentially serious side effects (that include tendon rupture, joint and muscle pain, confusion, and hallucinations) that may outweigh their benefits [20].

Chronic Rhinosinusitis

Chronic rhinosinusitis is a condition that is caused by persistent inflammation of the nasal and sinus mucosa. The understanding of this condition is still evolving. Infectious, environmental, and host factors are all thought to play a role in its genesis. As the name implies, the condition is generally managed rather than cured in most patients; thus, treatment options are usually limited to reduction of symptoms and improving overall quality of life. In cases where acute rhinosinusitis does not improve despite appropriate medical therapy options, or in cases where recurrent episodes of rhinosinusitis are problematic, otolaryngology referral may be warranted [2].

Tonsillitis and Pharyngitis

Tonsillitis is defined as inflammation of the tonsils, whereas pharyngitis is defined as inflammation of the pharynx. However, while the subjective complaint of sore throat is often clinically diagnosed as

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pharyngitis, there is no firm distinction between sore throat caused by tonsillitis and sore throat caused by pharyngitis [21]. Moreover, inflammation of either the tonsils or pharynx often leads to inflammation and swelling of multiple contiguous anatomic structure, including the adenoids and nasopharynx, to create the perception of odynophagia [22]. Therefore, for the remainder of this chapter, throat pain and discomfort will be referred to as *tonsillopharyngitis*.

Epidemiology

Acute tonsillopharyngitis accounts for approximately 14 million ambulatory care visits annually [23], as well as 6% of children's visits to pediatricians and family physicians [24]. The incidence of acute tonsillopharyngitis is most frequent in childhood before the age of 18 [31] and peaks during the winter and early spring [25]. The economic cost of group A streptococcal pharyngitis specifically in school-aged children has been estimated to range from $224 to $539 million per year [26].

Etiologies

Infectious

The most common causes of tonsillopharyngitis are respiratory viruses, including rhinovirus, influenza virus, parainfluenza virus, coronavirus, adenovirus, and respiratory syncytial virus [27]. Other viruses such as enteroviruses (coxsackievirus, echovirus), herpes simplex virus, and Epstein-Barr virus can also cause pharyngitis [27].

Bacteria may also cause acute tonsillopharyngitis, of which the most common cause is Group A β-hemolytic *Streptococcus* (GAS), accounting for 5–15% of adult cases of pharyngitis [28], and 15–30% of pediatric cases of pharyngitis [27]. Other bacterial causes include group C β-hemolytic *Streptococcus* (GCS), *Corynebacterium diphtheriae*, *Yersinia enterocolitica*, *Francisella tularensis*, and *Mycoplasma pneumoniae* [27]. *Neisseria gonorrhoeae* can also be a cause of acute pharyngitis, particularly in sexually active adolescents.

Fungal causes of tonsillopharyngitis are less common, though *Candida* species can cause thrush, which can lead to sore throat.

Inflammatory

Inflammatory causes of tonsillopharyngitis include chemical irritation, postnasal drip, allergic rhinitis, foreign body, mechanical trauma and injury (e.g., intubation), vocal cord granuloma, laryngopharyngeal reflux, and Kawasaki disease [29].

Clinical Presentation of GAS Tonsillopharyngitis

GAS tonsillopharyngitis classically presents with sudden onset of a sore throat and may be accompanied by headache, fever, abdominal pain, and nausea and vomiting [30]. Physical exam findings may include tonsillopharyngeal inflammation and patchy exudates, palatal petechiae, tender cervical lymphadenopathy, and a scarlatiniform rash [30].

Laboratory Diagnosis

There is considerable overlap between the clinical presentations of streptococcal and viral tonsillopharyngitis, and although scoring systems have been implemented to aid in identifying patients at low risk for streptococcal infection [31], laboratory confirmation is usually required for a definitive diagnosis. Thus, guidelines from the Infectious Disease Society of America (IDSA) recommend laboratory testing for GAS tonsillopharyngitis with rapid antigen detection test (RADT) and/or culture, **unless** clinical features suggesting viral infection are present (conjunctivitis, cough, rhinorrhea, oral ulcers, hoarseness) [30]. A negative RADT warrants a backup throat culture, as the sensitivity of RADT ranges from 70% to 90% compared to throat culture of 90–95%. However, a backup throat culture is not necessary with a positive RADT, since it has a high degree of specificity (95%) [30].

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Complications of GAS Tonsillopharyngitis

Suppurative Complications

Suppurative complications arise when GAS invades deeper adjacent tissues, resulting in infection and abscess formation. Peritonsillar abscesses are a potential complication of tonsillitis. This condition is one of the most common head and neck deep space infections, with an incidence of around 1 in 10,000 annually [32], most commonly seen in teenagers and young adults [33]. The abscess forms between the tonsil, the superior constrictor muscle, and the palatopharyngeal muscle [34]. Peritonsillar abscesses classically present with fever, odynophagia, erythema, trismus, deviation of the uvula, unilateral otalgia, drooling, and a muffled "hot potato" voice [34]. Significant odynophagia or impaired swallowing may result in dehydration. The diagnosis of peritonsillar abscess is primarily clinical, though CT scans and intra-oral ultrasounds can be used in certain circumstances, such as trismus limiting physical exam or in an uncooperative child [34]. Severe complications may occur if there is significant airway obstruction or further spread to adjacent regions (retropharyngeal abscess) [34]. Suspected spread of infection should be further assessed with MRI or CT with contrast.

Retropharyngeal abscesses are a potential complication of tonsillopharyngitis and most commonly occur in children between the ages of 2 and 4 years [45]. The most common clinical presentation includes neck pain, fever, odynophagia, and dysphagia following an upper respiratory infection [35]. Neck swelling may also be present, and depending on the degree of airway obstruction, there can also be a muffled "hot potato" voice, drooling, stridor, or tripod positioning. Initial management should be focused on maintaining the airway, as well as immediate consultation with an otolaryngologist, or if one is not immediately available, a person capable in obtaining and managing a difficult airway. Once the patient has been stabilized, a CT scan of the neck may be warranted for further evaluation [36].

Other potential suppurative complications of GAS tonsillopharyngitis include cervical lymphadenitis, acute otitis media, and impetigo [37].

Nonsuppurative Complications

Nonsuppurative complications of GAS tonsillopharyngitis are typically the results of post-infectious autoimmunity and include acute rheumatic fever, poststreptococcal reactive arthritis, Scarlet fever, acute glomerulonephritis, and pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS) [38].

Treatment of GAS Tonsillopharyngitis

Antibiotic therapy is the primary method of treatment for GAS tonsillopharyngitis. Penicillin or amoxicillin are considered first-line treatment options for GAS tonsillopharyngitis in most patients due to their efficacy, safety, narrow spectrum of activity, and low cost [39]. For patients without penicillin allergy, treatment options include either penicillin V orally (250 mg twice or three times daily for 10 days in children, 250 mg four times daily or 500 mg twice daily for 10 days in adolescents or adults) or amoxicillin orally (50 mg/kg once daily, maximum of 1000 mg/day for 10 days) [39]. For patients with penicillin allergy, treatment options include cephalexin orally (20 mg/kg/dose twice daily, maximum of 500 mg/dose for 10 days), cefadroxil orally (30 mg/kg once daily, maximum of 1 g/day) for 10 days, clindamycin orally (7 mg/kg/dose three times daily, maximum of 300 mg/dose) for 10 days, azithromycin orally (12 mg/kg once daily, maximum of 500 mg/day) for 5 days, or clarithromycin orally (7.5 mg/kg/dose twice daily, maximum of 250 mg/dose) for 10 days [39]. Research has not suggested one antibiotic regimen is superior to another [40].

Adjunctive treatment of GAS tonsillopharyngitis with nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen can be used supportively to relieve pain and fever, though aspirin should be avoided in children [39].

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Treatment of peritonsillar abscess primarily consists of incision and drainage alongside antibiotic coverage for both aerobic and anaerobic bacteria [41]. Empiric antibiotic therapy includes ampicillin-sulbactam intravenously (50 mg/kg/dose, maximum 3 g/dose every 6 h in children; 3 g every 6 h in adults) or clindamycin intravenously (13 mg/kg/dose, maximum 900 mg/dose every 8 h in children; 600 mg every 6–8 h in adults) [42]. Tonsillectomy is indicated in patients with peritonsillar abscess unresolved by incision and drainage, recurrent peritonsillar abscess, symptoms of sleep apnea, or multiple episodes of recurrent tonsillitis [41].

Treatment of retropharyngeal abscess primarily consists of antibiotic therapy against gram-positive aerobes and anaerobes [43]. Larger abscesses (>2.5 cm) or failure to respond to antibiotic therapy often warrants surgical incision and drainage [44].

Chronic Carriers and Asymptomatic Contacts

Chronic carriers may have GAS in their pharynx but do not have an immunologic response to the organism [45]. During winter and spring time in temperate climates, as many as 20% of school-aged children may be asymptomatic GAS carriers [46]. In these patients, testing and treatment with antibiotic therapy is generally not warranted, as carriers are unlikely to spread GAS, and even more unlikely to develop suppurative or non-suppurative complications [46, 47]. However, there are certain indications to treating asymptomatic carriers of GAS: any personal or family history of rheumatic fever, during outbreaks of acute rheumatic fever, or acute poststreptococcal glomerulonephritis, during outbreaks of GAS in closed/semi-closed communities (college campus, schools, military barracks, prisons, etc.), families with repeated episodes of GAS among family members, significant amount of anxiety about GAS among family members despite education and reassurance, or cases in which tonsillectomy is being considered due to chronic GAS carrier state [45].

Tonsillectomy

Tonsillectomy is the second-most common outpatient procedures performed on children in the United States [48]: the most recent report found that 289,000 tonsillectomies were performed in 2010 in children <15 years old [49]. Current guidelines outlined by the American Academy of Otolaryngology-Head and Neck Surgery Foundation recommend tonsillectomy in patients with at least seven episodes of recurrent tonsillopharyngitis in the past year, at least five episodes per year for 2 years, or at least three episodes per year for 3 years with documentation for each episode of tonsillopharyngitis with at least one of the following features: temperature >38.3 °C (101 °F), cervical lymphadenopathy, tonsillar exudate, or a positive test for GAS [50]. For patients who do not meet any of these criteria, watchful waiting is recommended [50].

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Sexually Transmitted Diseases

43

Courtney Kimi Suh

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General Principles

Definition/Background

Sexually transmitted infections (STIs) are of great healthcare and economic burden to the United States. In fact, most sexually active men and women will contract an STI at least once in their lifetime [1]. According to 2008 US estimates, STIs resulted in 16 billion dollars of direct medical costs [2]. Additionally, 19.7 million new infections occurred, with 50% occurring in individuals 15–24 years of age [3]. Overall, human papillomavirus (HPV) is the most common sexually transmitted infection. Other common infections include chlamydia, gonorrhea, hepatitis B virus, herpes simplex virus type 2 (HSV-2), human immunodeficiency virus (HIV), syphilis, and trichomoniasis [1]. Chlamydia, gonorrhea, and syphilis infection rates continue to increase in numbers over the years although this may be related to improve screening practices [4]. Family physicians have a responsibility to improve prevention, detection, and treatment of STIs in order to decrease transmission and prevent subsequent morbidity and mortality.

Chlamydial Infection

Chlamydia is a sexually transmitted infection caused by *Chlamydia trachomatis*, which can infect the cervix, urethra, rectum, lung, and eye. Chlamydia is a frequent cause of pelvic inflammatory disease (PID), infertility, chronic pelvic pain, and ectopic pregnancy and may facilitate the transmission of HIV in women. In men, chlamydia commonly leads to epididymitis and orchitis [5]. Chlamydia continues to be the most commonly reported STI in the United States since 1994, with approximately 1.8 million cases in 2018. Females have higher rates of infection

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and, in both genders, the highest rates of infections occur in the 15–24-year age group [4].

Screening

The CDC recommends that all sexually active women younger than 25, and older women with risk factors, such as multiple or new sexual partners, be screened annually. In addition, all pregnant women younger than 25, and older women with risk factors should be screened early in pregnancy and then rescreened during the third trimester. The CDC recommends annual screening for men who have sex with men (MSM) [6]. There is insufficient evidence to recommend routine screening in sexually active men who have sex with women [7].

Clinical Presentation

Female patients may complain of vaginal discharge, bleeding, or dysuria; however, most chlamydia infections are asymptomatic. Physical exam may reveal mucopurulent or purulent discharge with or without a friable cervix; however, a normal exam does not exclude infection. Male patients are also predominantly asymptomatic, with only 2–4% of infected men reporting symptoms such as penile discharge, pruritus, or dysuria. Male and female patients who have receptive anal intercourse may present with rectal pain, discharge, or bleeding [5]. Additionally, male and female patients who engage in orogenital sex may have pharyngeal infection, but symptoms are rare [8].

Diagnosis

In women, diagnostic testing can be performed through endocervical samples, provider or patient-collected vaginal samples, or urine specimens. In men, specimens from a urethral swab or urine sample are sufficient. Pharyngeal and rectal specimens can also be taken for cell culture when appropriate. Nucleic acid amplification testing (NAAT) is the most sensitive testing available and can be used on almost all specimens; however, research is still in progress to confirm the efficacy of NAAT in pharyngeal and rectal swabs. NAAT, cell culture, direct immunofluorescence, EIA, and nucleic acid hybridization can all be used on endocervical and urethral samples. All documented chlamydia infections must be reported to the CDC.

Treatment

Patients should be treated for chlamydia immediately after diagnosis of chlamydia or gonorrhea for presumed coinfection with chlamydia. Patients should be instructed to abstain from sex for 7 days after completion of therapy and until sexual partner(s) have also been treated adequately. Ideally, the antibiotics should be available to the patient at the physician's office, and the first dose should be directly observed. Patients who are likely to fail to comply with a 7-day course of treatment should receive single-dose treatment. All patients who test positive for chlamydia should also be evaluated for other sexually transmitted infections such as gonorrhea, syphilis, and HIV and instructed on the need for repeat testing for chlamydia in 3 months to identify reinfection. Repeat testing for chlamydia earlier than 3 weeks after treatment is not recommended because of the persistence of nonviable antigen leading to falsely positive results [7] (Table 1).

Table 1 Treatment of Chlamydia Trachomatis

Preferred regimen	Dosage	Instructions	Duration
Azithromycin	1 g	By mouth in a single dose	1 day
Doxycycline	100 mg	By mouth twice daily	7 days
Alternative regimen			
Erythromycin ethyl succinate	800 mg	By mouth four times daily	7 days
Levofloxacin	500 mg	By mouth once daily	7 days
Ofloxacin	300 mg	By mouth twice daily	7 days

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Pregnancy

Pregnant women with chlamydia can be treated safely with azithromycin or the alternative erythromycin dosing if needed. Additionally, infected pregnant patients should be retested 3 weeks after treatment for a test of cure. She should also undergo repeat testing in 3 months and again in the third trimester of pregnancy if risk factors are present [7].

Sexual Partners

Ideally, the patient's sexual partner should undergo clinical evaluation, testing, and counseling regarding STIs in addition to antibiotic therapy. However, in certain circumstances, the family physician may consider implementing Expedited Partner Therapy (EPT). EPT is the clinical practice of treating sexual partners with prescriptions or medications without requiring a clinical examination or testing. This is particularly useful when sexual partners will not obtain appropriate medical care for any reason. The option to use EPT is legal in most states within the United States; however, a family physician must check their own state law prior to engaging in EPT. Additionally, EPT should only be utilized in very selective cases in the MSM population due to the risk of concurrent undiagnosed HIV and should never be used in partners who may be at risk for severe infections [9].

Gonorrhea

Gonorrhea infection is caused by the bacteria *Neisseria gonorrhoeae*, a Gram-negative diplococcus. Gonorrhea can cause urogenital, anorectal, pharyngeal, and conjunctival infections [4]. Like chlamydia, it can lead to PID and its complications and increase the risk of transmission of HIV in women [10]. Additionally, *N. gonorrhoeae* can cause disseminated gonococcal infections and, rarely, endocarditis and meningitis [4]. Even more concerning, gonorrhea is becoming resistant to fluoroquinolones and cefixime, limiting options for treatments [11, 12]. There were 583,405 cases of gonorrhea reported in the United States in 2018, making it the second most common reported STI [4]. There is a higher number of cases in men than women. This infection occurs most commonly in persons between the ages of 15 and 24 years.

Screening

The CDC recommends that all sexually active women under 25 years of age and sexually active women 25 and older with risk factors, such as multiple or new sexual partners, be screened annually [4]. In addition, all pregnant women under 25 years of age or 25 and older with risk factors should be screened at least once in pregnancy. The CDC recommends annual screening for men who have sex with men (MSM) but makes no recommendation regarding men who have sex with women [7].

Clinical Presentation

Like chlamydia, gonorrhea is often asymptomatic in women. Women may present with vaginal discharge, dysuria, pelvic pain, or frequent heavy menses. Physical exam may reveal mucopurulent discharge, cervicitis, or adnexal or cervical tenderness. Unlike chlamydia, 90% of men with gonorrhea exhibit symptoms including dysuria, penile discharge, or epididymitis. A rectal infection can be asymptomatic or result in anal pruritus, rectal pain, mucopurulent discharge, and tenesmus. A pharyngeal infection from oral sex can cause pharyngeal symptoms. Disseminated gonococcal infection affects 0.4–3% of patients with gonorrhea. Patients may present with asymmetric joint pain and swelling along with a skin rash. In rare cases, untreated disease progression causes perihepatitis, meningitis, or endocarditis [10].

Diagnosis

Neisseria gonorrhoeae can be detected by culture and nucleic acid hybridization tests (NAAT) with

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female endocervical and male urethral swab specimens. NAATs can be used to detect infection in the above samples as well as provider or self-collected vaginal swabs and urine specimens. NAATs are not FDA approved for use in the rectum, pharynx, and conjunctiva; however, some NAATs are used in certain specialty laboratories due to their superior sensitivity over culture. In cases of suspected treatment failure, a culture must be performed to determine bacterial sensitivities. All documented gonorrheal infections must be reported to the CDC [7].

Treatment

Patients should be treated for gonorrhea immediately after diagnosis and also screened for chlamydia, syphilis, and HIV. Patients should be instructed to abstain from sex until completion of treatment and resolution of symptoms in both the patient and their sexual partner(s). The antibiotics should be available to the patient at the physician's office, and the first dose should be directly observed. All patients who test positive for gonorrhea should be treated for possible coinfection with chlamydia. Infected individuals should also be evaluated for other sexually transmitted infections such as HIV and syphilis and instructed on the need for repeat testing for gonorrhea in 3 months to identify reinfection. If there is concern for treatment failure, a culture must be checked in order to confirm antibiotic susceptibility. If treatment failure is discovered, the case should be discussed with the local health department [7].

Because of emerging antibiotic resistance, the preferred treatment option for patients infected with gonorrhea is ceftriaxone 500 mg intramuscularly in one dose with the addition of azithromycin 1 g orally in a single dose. If the patient is allergic to azithromycin, he or she can take doxycycline 100 mg by mouth twice daily for 7 days as an alternative. If ceftriaxone cannot be used, there are two alternative options: cefixime 400 mg orally in one dose with either azithromycin 1 g orally in one dose or doxycycline 100 mg orally twice daily for 7 days or azithromycin 2 g orally alone in a single dose (although this is not preferred due to increasing drug resistance). These dosing regimens also include treatment for likely coinfection with chlamydia [7].

Penicillin/Cephalosporin Allergy

For a patient that has an allergy to cephalosporins or an EgE-mediated penicillin allergy, data on alternative therapeutic options are limited. Options include dual treatment with a single dose of oral gemifloxacin 320 mg plus a single dose of oral azithromycin 2 grams. In these cases, it is best to consult with an infectious disease specialist [7, 12].

Pregnancy

Infected pregnant women should be treated with the recommended or alternative dosing of a cephalosporin as well as concurrent treatment with azithromycin for presumptive coinfection with chlamydia. If the patient cannot tolerate a cephalosporin, consultation with an infectious disease specialist is recommended [7].

Sexual Partners

The patient's last sexual partner or any partners within 60 days prior to symptoms must be empirically treated for gonorrhea and chlamydia. Partners should undergo clinical evaluation, testing, and counseling regarding STIs in addition to treatment; however, they may be eligible for EPT [9]. Since the preferred treatment requires an intramuscular injection of ceftriaxone, partners can be treated with an alternative therapy of cefixime 400 mg and azithromycin 1 g [9]. Similar to chlamydia, EPT should only be utilized in very selective cases. EPT should not be used in populations at high risk for HIV such as MSM with gonorrhea and should never be used in partners who are exhibiting signs of more severe infection [7].

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Trichomoniasis

Trichomoniasis, caused by the protozoan *Trichomonas vaginalis*, is the most common nonviral sexually transmitted infection in the world [13]. An estimated 3.7 million people in the United States are infected but only 30% develop symptoms of infection [7]. Although asymptomatic, trichomonas can result in infertility, pelvic inflammatory disease, and adverse birth outcomes in infected pregnant women. In addition like gonorrhea and chlamydia, trichomoniasis increases the sexual transmission of HIV, at least doubling the risk of acquiring HIV infection [13].

Screening

The CDC recommends screening for trichomonas in women with risk factors such as history of new or multiple partners, sexually transmitted infections, exchanging sex for payment, or injecting drugs or women receiving care at STI clinics or correctional facilities [6].

Clinical Presentation

Often, men infected with trichomonas exhibit no symptoms; however, they may present with nongonococcal urethritis. Women may complain of malodorous yellow-green vaginal discharge with associated vulvar irritation; however, most remain asymptomatic [7].

Diagnosis

For women, trichomoniasis may be diagnosed through direct microscopy of a wet prep of vaginal secretions; however, this is only 50–60% sensitive. NAAT is highly sensitive and can be run on vaginal, endocervical, or urine specimens from women and urethral swabs or urine from men. Two point-of-care vaginal swab tests are available: OSOM Trichomonas Rapid Test uses immunochromatographic technology and Affirm VP III uses DNA hybridization, both with sensitivities of >83%. *T. vaginalis* can also be detected through culture of vaginal secretions, liquid-based pap cytology, and NAAT or PCR of vaginal, endocervical, or urine specimens although this is no longer the gold standard. In men, urethral swab, urine, or semen can be cultured; however, NAATs as discussed above can be used to detect *T. vaginalis* in men with superior sensitivity [7].

Treatment

Patients who test positive for trichomonas should be tested for other sexually transmitted infections including HIV. Trichomonas is treated with metronidazole 2 g by mouth in a single dose or tinidazole 2 g by mouth in a single dose. An alternative treatment is to give metronidazole 500 mg by mouth twice daily for 7 days. Topical metronidazole is not an acceptable option, as it does not reach appropriate therapeutic levels. Patients should be instructed to abstain from sex until completion of treatment and resolution of symptoms in both the patient and their sexual partner(s). Although retesting for trichomonas 3 months after treatment can be considered in women, there are no guidelines recommending this. If *T. vaginalis* persists despite treatment with metronidazole and it is not due to reinfection, it should be considered to be resistant, which happens in 4–10% of cases in vaginal trichomoniasis. If a patient fails metronidazole 2-g single-dose treatment, the patient can be treated with metronidazole 500 mg orally twice daily for 7 days. If patients fail this treatment, they should be given tinidazole or metronidazole at 2 g orally daily for 7 days. Failure to respond to these treatments may require specialty consultation.

In addition, patients with a critical allergy to nitroimidazoles, which include both metronidazole and tinidazole, must undergo desensitization [7].

Pregnancy

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and

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low birth weight. Women can be treated with 2 g metronidazole in a single dose at any stage of pregnancy. Unfortunately, treatment with metronidazole has not been shown to reduce adverse birth outcomes, and, in fact, some limited data shows a possibility of increased prematurity or low birth weight after treatment with metronidazole [14, 15]. Treatment should be offered to prevent respiratory or genital infection of the newborn as well as further transmission to sexual partners; however, therapy can be deferred until after 37 weeks of gestation in asymptomatic women [7].

Sexual Partners

As with gonorrhea and chlamydia, the patient's sexual partner should undergo clinical evaluation, testing, and counseling regarding STIs in addition to treatment; Expedited Partner Therapy can be considered if necessary [9].

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is characterized by inflammation of the upper genital tract in the female, which can include endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. It was previously one of the most common gynecologic reasons for inpatient hospital admission in the United States, but improved outpatient and emergency room treatment has decreased the need for hospital admission [16].

Multiple organisms have been implicated in PID, often including *N. gonorrhea* and *C. trachomatis*. More recently, other organisms are also involved including *G. vaginalis*, *H. influenzae*, enteric Gram-negative rods, *S. agalactiae*, cytomegalovirus, *M. hominis*, *U. urealyticum*, and possibly *M. genitalium* most likely beginning with an ascending infection originating in the cervix and creating the opportunity for entry of other organisms [7, 16]. It is important to recognize PID in its early stages to avoid complications such as tubo-ovarian abscess, pelvic peritonitis, and long-term sequelae [7]. About 20% of women with PID become infertile, 40% develop chronic pain, and 1% of those who do conceive have an ectopic pregnancy [16].

Clinical Presentation

Women may present with a wide range of symptoms ranging from no symptoms to vaginal bleeding or discharge to pelvic pain [6, 16].

Diagnosis

The diagnosis is typically made clinically. On exam, the patient should have at least cervical motion tenderness, uterine tenderness, or adnexal tenderness. Leukorrhea, vaginal discharge, cervical exudate, cervical friability, temperature $> 101\ ^{\circ}F$ ($38.3\ ^{\circ}C$), and elevated ESR or CRP are often seen. Known gonorrhea or chlamydia infection may also assist in making the diagnosis. However, because of the potentially severe consequences of untreated PID, these criteria are not required to make a clinical diagnosis. Sometimes, symptoms can present subtly, and the condition can have an indolent course. In cases requiring more invasive testing, PID may be diagnosed through ultrasound or MRI imaging showing thickened and fluid-filled Fallopian tubes or a tubo-ovarian complex, histopathology demonstrating endometritis, or laparoscopy showing abnormalities consistent with PID. Of note, negative cervical cultures do not exclude PID, as cultures may not be positive with upper reproductive tract disease [7].

Treatment

All women diagnosed with PID should be tested for gonorrhea and chlamydia as well as HIV. Women with PID can be treated in the outpatient setting unless they have signs of severe infection including nausea, vomiting, or high fever, are pregnant, cannot tolerate or have failed oral antibiotic therapy, have a tubo-ovarian abscess, or need observation to rule out a possible surgical

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emergency. Those who require hospitalization should receive parenteral antibiotic therapy for 24–48 h after clinical improvement. Those with a tubo-ovarian abscess should be observed for at least 24 h. Options for parenteral treatment are listed in Table 2 [7].

Parenteral Treatment

All other patients can be treated in an outpatient setting with similar efficacy. If a patient fails to improve after 72 h, they should be reevaluated to reconfirm PID as the cause of their symptoms and then treated with parenteral antibiotics. Options for outpatient treatment are listed in Table 3 [7].

Table 2 Parenteral Treatment of Pelvic Inflammatory Disease

Recommended regimen	Subsequent oral therapy	Tubo-ovarian abscess present
Cefotetan 2 g IV every 12 h *or* Cefoxitin 2 g IV every 6 h *and* Doxycycline 100 mg PO/IV every 12 h	Doxycycline 100 mg every 12 h for a total of 14 days	Add oral clindamycin 450 mg every 6 h for a total of 14 days *or* Metronidazole 500 mg every 12 h for a total of 14 days
Clindamycin 900 mg IV every 8 h *and* Gentamicin at 2 mg/kg of body weight in an IV or IM loading dose, followed by 1.5 mg/kg every 8 h	Doxycycline 100 mg orally twice daily for a total of 14 days *or* Clindamycin 450 mg four times daily for a total of 14 days	Choose clindamycin over doxycycline for subsequent oral therapy: Clindamycin 450 mg four times daily for a total of 14 days
Alternative therapy		
Ampicillin/sulbactam 3 g IV every 6 h *and* Doxycycline 100 mg orally or IV every 12 h	Doxycycline 100 mg orally twice daily for a total of 14 days	Add oral clindamycin 450 mg every 6 h for a total of 14 days *or* Metronidazole 500 mg every 12 h for a total of 14 days

See Ref. [7]

Outpatient Treatment Options

Patients who are treated for PID should also be tested for HIV. If a patient tests positive for gonorrhea or chlamydia, he or she should be retested 3–6 months after treatment.

Penicillin Allergy

If a patient has a severe penicillin allergy and cannot take a cephalosporin, the patient can be treated with parenteral therapy or given a course of fluoroquinolone Table 4, particularly if community prevalence and individual risk for gonorrhea is low and follow-up is likely. This is not ideal given the emergence of quinolone-resistant *Neisseria gonorrhoeae*. Patients should be cultured for gonorrhea prior to treatment in order to

Table 3 Outpatient Treatment of Pelvic Inflammatory Disease

Recommended regimen	Additional anaerobic coverage
Ceftriaxone 500 mg IM in a single dose *and* Doxycycline 100 mg PO twice daily for 14 days	+/− Metronidazole 500 mg PO twice daily for 14 days
Cefoxitin 2 g IM in a single dose *and* Probenecid 1 g PO in a single dose *and* Doxycycline 100 mg PO twice daily for 14 days	+/− Metronidazole 500 mg PO twice daily for 14 days
Parenteral third-generation cephalosporin (ceftizoxime or cefotaxime) *and* Doxycycline 100 mg PO twice daily for 14 days	+/− Metronidazole 500 mg PO twice daily for 14 days
Alternative	**Additional anaerobic coverage**
Ceftriaxone 500 mg IM in a single dose *and* Azithromycin 1 g PO once a week for 2 weeks	+/− Metronidazole 500 mg PO twice daily for 14 days

See Ref. [7]

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Table 4 Treatment of *N. gonorrhoeae* in Patients with Severe Penicillin/Cephalosporin Allergy [7]

PCN allergic recommendation	Additional anaerobic coverage	If *N. gonorrhoeae* present is quinolone-resistant or has unknown susceptibility
Levofloxacin 500 mg orally once daily for 14 days *or* Ofloxacin 400 mg twice daily for 14 days *or* Moxifloxacin 400 mg orally once daily	+/− Metronidazole 500 mg PO twice daily for 14 days	Add azithromycin 2 g orally as a single dose

See Ref. [7]

determine susceptibilities. If the isolate is quinolone-resistant or susceptibilities are not available, consult with an infectious disease specialist [7].

Sexual Partners

The patient's last sexual partner or any partners within 60 days prior to symptoms must be tested and also empirically treated for gonorrhea and chlamydia [7].

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum*. Rates of syphilis dropped to their nadir in 2000; however, rates have been increasing since then. In 2018, a total of 35,063 cases of primary and secondary syphilis were reported to the CDC, with 86% of these cases occurring in men. Of males who are affected, most are men who have sex with men and men who have sex with both men and women [4, 17].

Screening

The CDC recommends screening of all pregnant women at their first prenatal visit and then retesting in the early third trimester and at delivery if at high risk. Additionally, the CDC recommends testing at least annually for sexually active MSM and every 3–6 months in high risk MSM [6].

Clinical Presentation

Primary Syphilis

A patient infected with syphilis may present with a painless chancre at the site of inoculation anywhere from 10 to 90 days after infection. The chancre typically progresses from a macule to a papule to an ulcer with a clean base, and multiple lesions may occur. These lesions will resolve without treatment in 3–6 weeks. The patient may also demonstrate regional bilateral rubbery and painless lymphadenopathy [17].

Secondary Syphilis

The lesions of secondary syphilis occur several weeks after the primary chancre appears and may persist for weeks to months. There may be overlap between primary and secondary stages. Patients most commonly present with non-pruritic maculopapular skin rash involving the palms and soles; flat patches of mucocutaneous lesions in the oropharynx, larynx, and genitals; and lymphadenopathy. Patients may also demonstrate condyloma lata, which are heaped-up, wartlike papules in warm intertriginous areas. Infection can involve the liver and kidney with occasional splenomegaly. Alopecia, typically in a patchy "moth-eaten" pattern, may be seen [17].

Tertiary Syphilis

Although progression to tertiary syphilis remains rare, failure to consider the diagnosis is common. Late syphilis can occur within 1–20 years of infection and is characterized by gummatous syphilis, cardiovascular problems, or CNS disease. Gummas are granulomatous lesions that destroy mucosa, soft tissue, cartilage, bone, eye,

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and viscera. Cardiovascular complications include ascending aortic aneurysm, aortic insufficiency, or coronary ostial stenosis [17].

Neurosyphilis

Neurosyphilis occurs when *T. pallidum* spreads to the central nervous system, can occur at any stage of syphilis, and may be asymptomatic. Neurosyphilis can be divided into early and late stages. Early neurosyphilis can occur months to a few years after infection, presenting with acute syphilitic meningitis or meningovascular syphilis. Late neurosyphilis occurs decades after infection and may present as general paresis or tabes dorsalis. Ocular involvement can occur at any stage of neurosyphilis [17].

Latent Syphilis

Latent syphilis occurs when the host suppresses the infection so that no clinical signs or symptoms are apparent and serology is positive for syphilis. This can occur at any point within the primary and secondary stages of syphilis. Latent syphilis is categorized as early latent syphilis, late latent syphilis, or latent syphilis of unknown duration. Early latent infection denotes syphilis infection of less than 1-year duration. In order to classify a patient as having early latent syphilis, certain criteria must be met to assure that infection occurred within the past 1 year. If there has been previous serologic testing within the past year, there must be either seroconversion from previously negative results or a fourfold increase in titer. Additionally, latent syphilis can be categorized as early if the patient exhibited unequivocal symptoms of primary or secondary syphilis within the past year and initiated sexual contact with a confirmed infectious case of syphilis within the past year or the only possible sexual exposure occurred within the past year. Late latent syphilis, on the other hand, is infection that has been present for greater than 1 year. If there is uncertainty about the duration of latent syphilis, it is classified as latent syphilis of unknown duration, and treatment guidelines for late latent syphilis should be followed. Syphilis is much less sexually transmissible in the latent phase [17].

Diagnosis

Definitive diagnosis of syphilis is through darkfield examination of lesion exudate or tissue for *T. pallidum*. Presumptive diagnosis is also possible through the use of serologic testing; however, serologic testing may not be positive in early stages of primary syphilis. Additionally, both nontreponemal and treponemal tests must be used in conjunction in order to avoid false-positive results. Although the CDC recommends initial testing beginning with nontreponemal tests such as Venereal Disease Research Laboratory (VDRL) or RPR, some labs implement initial testing through treponemal tests. Because of the high rate of false positives, particularly in those with autoimmune conditions, older age, and injection drug users, positive nontreponemal tests must be confirmed with treponemal tests such as fluorescent treponemal antibody absorbed (FTA-ABS) tests, *T. pallidum* passive particle agglutination (TP-PA) assay, various EIAs, and chemiluminescence immunoassays. Nontreponemal tests are reported quantitatively which allows for identification of disease activity, reinfection, and response to treatment through trends in titers, which may eventually decline to become nonreactive over time. In contrast, treponemal tests should not be used to evaluate disease activity or treatment response, as the test will likely remain reactive regardless of treatment. Serologic testing cannot be used to reliably distinguish between stages of syphilis. All positive tests must be reported to local or state health departments [7].

Treatment

Primary and Secondary Syphilis

All stages of syphilis are preferentially treated with parenteral penicillin G. Primary and secondary syphilis in nonpregnant adults is treated with a one-time dose of benzathine penicillin G 2.4 million units intramuscularly. Within 24 h after treatment, patients may experience the Jarisch–Herxheimer reaction, an acute febrile illness with

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associated headache, myalgia, fever, or other symptoms, which can be treated symptomatically with fever and pain reducers as needed. In addition, all patients with syphilis should be tested for HIV infection. To assure appropriate treatment, patients need to have repeat evaluation and serology 6 and 12 months following treatment to assure a fourfold decrease in nontreponemal titer. In patients with an inadequate treatment response, the clinician should consider additional clinical and serologic follow-up, retreatment with weekly penicillin G 2.4 million units intramuscularly for 3 weeks, retesting for HIV, and CSF analysis [7].

If a patient is penicillin allergic and not pregnant, treatment with doxycycline 100 mg orally twice daily for 14 days or tetracycline 500 mg four times daily for 14 days is appropriate. Ceftriaxone 1 g daily IM or IV for 10–14 days may be an effective treatment for early syphilis. Azithromycin in a single 2 g oral dose is effective for treating early syphilis; however, due to resistance patterns, it should only be used when penicillin or doxycycline treatment is not feasible [7].

Tertiary Syphilis

Tertiary syphilis should be treated with benzathine penicillin G 2.4 million units intramuscularly given at 1-week intervals for a total of three doses. Before treatment, patients affected with tertiary syphilis should undergo a CSF examination. Guidelines for further follow-up of these patients vary; infectious disease consultation might be considered in these cases [7].

Neurosyphilis

Neurosyphilis is treated with aqueous crystalline penicillin G 3–4 million units IV every 4 h or 18–24 million units daily through continuous infusion for 10–14 days. There is also an alternative regimen of procaine penicillin 2.4 million units IM once daily with probenecid 400 mg orally four times daily for 10–14 days. After completion of this initial 10–14 days of treatment, patients may also receive additional benzathine penicillin 2.4 million units IM once per week for up to 3 weeks. All patients with neurosyphilis must be tested for HIV. Follow-up CSF studies to document a decrease in leukocytes must be completed at 6-month intervals to assure treatment response. The CSF cell count and protein should be normal after 2 years. If a patient is penicillin allergic, ceftriaxone 2 g IV or IM daily for 10–14 days is administered. If the patient cannot receive ceftriaxone due to cross-reactivity or other reasons, the patient must be desensitized [7].

Latent Syphilis

Early latent syphilis should be treated with benzathine penicillin G 2.4 million units intramuscularly in a single dose. Late latent syphilis or latent syphilis of unknown duration should be treated with benzathine penicillin G 2.4 million units intramuscularly given at 1-week intervals for a total of three doses. The management of a patient who misses one of the weekly doses of benzathine penicillin is unclear; however, current guidelines suggest that 10–14 days between benzathine penicillin doses may be acceptable. If intervals are longer than 14 days, the entire course of therapy must be restarted. Additionally, if the patient is pregnant and misses any of the three doses of penicillin, she must restart the entire course of therapy in order to reduce the possibility of transmitting syphilis to the fetus. If a nonpregnant patient with early latent syphilis is penicillin allergic, the patient may be treated with doxycycline 100 mg orally twice daily for 14 days or tetracycline 500 mg four times daily for 14 days. If the nonpregnant penicillin-allergic patient has late latent syphilis or latent syphilis of unknown duration, the patient should be treated with doxycycline 100 mg orally twice daily or tetracycline 500 mg orally four times daily for 28 days. Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. If the titers increase fourfold, a high titer ($>$1:32) fails to decline at least fourfold in this time period, or if clinical signs of syphilis emerge, the patients must undergo CSF examination and be retreated for latent syphilis [7].

Pregnancy

In order to prevent congenital syphilis in the fetus, all pregnant patients must be treated with

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penicillin as indicated above based on her stage of syphilis. If a pregnant patient is penicillin allergic, she must be desensitized and treated with the appropriate dosing regimen of penicillin.

Sexual Partners

Any sexual partner of a patient diagnosed with syphilis should be evaluated clinically and serologically. Because early stages of primary syphilis may be seronegative, partners of patients with syphilis who were exposed within 90 days preceding the diagnosis of primary, secondary, early latent, or latent syphilis of unknown duration with a high nontreponemal titer ($\geq$1:32) should be treated presumptively. If it has been greater than 90 days since exposure through sexual contact with a patient diagnosed with primary, secondary, early latent, or latent syphilis of unknown duration with a high nontreponemal titer ($\geq$1:32), the partner should be presumptively treated if serologic testing is not immediately available and follow-up is uncertain. In all other cases, the patient can be treated based on clinical and serologic findings. For the purposes of treatment of partners only, latent syphilis of unknown duration can be assumed to be early latent disease if titers are high. Long-term sex partners of patients with latent syphilis can be evaluated clinically and serologically for syphilis and treated based on their results [7].

Genital Warts

Genital warts affect 1% of all sexually active men and women in the United States. Human papillomavirus or HPV causes genital warts, and 90% of genital warts are caused by HPV 6 or 11 [18]. Genital warts are transmitted through vaginal, anal, and oral contact and can be transmitted even if there are no visible warts [7]. Genital warts are highly contagious, as approximately 2/3 of sexual partners will develop clinical genital warts within 9 months of sexual contact [19].

Clinical Presentation

While genital warts are typically asymptomatic, patients may complain of pain or pruritus at the sites of the warts. Genital warts appear as flat papular lesions or pedunculated cauliflower-like growths on the anogenital mucosa [18].

Diagnosis

Diagnosis of genital warts is clinical, but a biopsy can be taken for definitive diagnosis if the patient is immunocompromised; if the lesions are atypical, pigmented, indurated, fixed, bleeding, or ulcerated; or if they worsen or fail to improve with standard treatment [7].

Treatment

Genital warts are treated for resolution of symptoms or for cosmetic concerns. While treatment is not definitive, it will often result in wart-free periods. Additionally, although treatment of warts has been shown to reduce HPV viral load, no studies have demonstrated that this reduces transmission to uninfected partners [7]. When left untreated, warts may resolve, remain the same in appearance, or increase in size and number [7].

There are multiple topical treatment modalities for genital warts; these can be divided into patient-applied (Table 5) and provider-applied (Table 6), listed below. Clinicians can determine which method is most beneficial based on wart size, location, patient preference, and cost. Most genital warts respond within 3 months of therapy. Follow-up visits facilitate the assessment of the response to treatment. Side effects of treatment include hypo- or hyperpigmentation, scarring, chronic pain, and rarely systemic effects [7].

Topical Condyloma Treatments: Patient Applied

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Table 5 Patient Applied Treatment for Condyloma [7]

Treatment	Instructions	Reapplication/ duration	Side effect	Special considerations	Safety in pregnancy
Podofilox 0.5% solution or gel	Apply twice daily for 3 days followed by 4 treatment-free days	Repeat as needed for up to 4 cycles	Mild to moderate pain or local irritation	Wart area must be less than 10 cm^2, and volume of podofilox used must be 0.5 mL or less per day	Contraindicated
Imiquimod 3.75% or 5% cream	Once daily at bedtime three times a week; washed off 6–10 h after application	Treatment for maximum of 16 weeks	Redness, irritation, induration, ulceration/ erosion, and vesicles		Uncertain
Sinecatechin 15% ointment	Apply 0.5 cm strand of ointment to each wart three times daily	Treatment for maximum of 16 weeks	Erythema, pruritus/ burning, pain, ulceration, edema, induration, and vesicular rash	Avoid sexual contact while ointment is applied Not recommended for HIV-infected persons, immunocompromised persons, or persons with clinical genital herpes	Uncertain

Table 6 Physician Applied Treatment for Condyloma [7]

Treatment	Application instructions	Interval	Special considerations	Side effect	Safety in pregnancy
Cryotherapy with liquid nitrogen	May be used with topical or injected local anesthesia as needed	Every 1–2 weeks		Immediate pain, subsequent necrosis, and blistering	Safe
Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90%	Apply a small amount to wart; allow to dry fully (denoted by white frosting) before patient sits or stands	Every week as needed	Neutralize with soap or sodium bicarbonate if pain is intense. Use powdered talc, sodium bicarbonate, or liquid soap preparations if excess is applied		Unknown
Surgical removal by trained provider	Local anesthesia, electrocautery, or tangential excision with fine scissors or scalpel, laser, or curettage		Surgical therapy is most beneficial for patients who have a large number or area of genital warts		Safe

Topical Condyloma Treatments: Provider Applied

See Ref. [7]

Alternative regimens include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. These treatment options presently have insufficient data and more side effects. Cervical warts must be biopsied to exclude high-grade squamous intraepithelial lesion, and there are other treatment

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recommendations for warts located in the urethral meatus, vagina, and anus [7].

Pregnancy

Pregnant patients with genital warts have limited options for treatment. Pregnant patients with genital warts can proceed through typical prenatal care and delivery; however, cesarean may be required for genital warts which may obstruct the pelvic outlet or cause excessive bleeding during vaginal delivery. Pregnant patients should be informed that rarely the HPV subtypes 6 and 11 associated with genital warts could be passed on to offspring, causing respiratory papillomatosis. It is uncertain exactly how the virus is transmitted from the mother; therefore, there are currently no recommendations to prevent transmission [7].

Prevention

As with all sexually transmitted infections, HPV infection and genital warts can be prevented through abstinence or limitation of the number of sexual partners. Condoms are not fully protective against HPV because all genital areas are not completely covered by a condom. The quadrivalent human papillomavirus vaccine is active against most subtypes of HPV that cause genital warts in men and women [7].

Genital Herpes

Herpes simplex virus (HSV) 1 or 2 causes genital herpes, although most recurrent genital infections are caused by HSV-2. More than 50 million people in the United States suffer from HSV-2. Once contracted, HSV is a chronic lifelong illness with varying number of reoccurrences and intermittent viral shedding [7]. HSV infection increases the risk of HIV acquisition two- to fourfold due to the presence of open ulcerations in the mucosa. Rarely, HSV can result in disseminated infection, pneumonitis, hepatitis, blindness, encephalitis, and aseptic meningitis. The chronicity of HSV often causes psychological distress and stigma [20].

Screening

General screening for genital herpes is not recommended [7].

Clinical Presentation

Most patients have no or only mild symptoms. 87% of infected individuals are unaware of being infected. Patients may notice one or more vesicles on the mucosa of the genitals, rectum, or mouth, which eventually ulcerate. These ulcerations may take 2–4 weeks to heal. Incubation after exposure ranges from 2 to 12 days; the primary outbreak is usually longer with more systemic symptoms of malaise, fever, and lymphadenopathy. Subsequent outbreaks may be preceded by hours to days of a prodromal tingling or shooting pains in the legs, hips, and buttocks before appearance of lesions [20].

Diagnosis

If a patient has a genital ulcer or mucocutaneous lesion, cell culture or polymerase chain reaction assay (PCR) should be taken from a vesicle. PCR assays are the most sensitive and can be used to determine the presence of HSV1 or HSV2. Because viral shedding is intermittent, a negative culture or PCR does not exclude a diagnosis of HSV infection. A patient's serum can also be tested for type-specific serum antibodies to HSV 1 or 2. Positive HSV-1 serum antibodies may be caused by a previous oral infection that often occurs in childhood, but it can also indicate genital HSV. Patients with HSV-2 are more likely to have recurrences and have increased occurrences of asymptomatic viral shedding. Serum antibody testing is useful if a patient has suspected HSV due to symptoms but has a negative PCR or culture. It can also be instructive if the patient has a clinical diagnosis of genital

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herpes but no history of laboratory confirmation. Finally, it provides useful information for patients that have a sexual partner with known HSV. Screening of the general population for HSV-1 and 2 is not recommended [7].

Treatment

Antiviral therapy can be given for suppression or treatment of individual episodes. There is no treatment available to completely eradicate latent virus or alter the course of recurrences after medication is discontinued [7].

A patient's first clinical episode of genital herpes should be treated with antiviral therapy due to the severity and length of symptoms. Patients may have severe genital ulcers and systemic or neurologic involvement. Treatment options for immune-competent individuals include acyclovir 400 mg orally three times daily, acyclovir 200 mg orally five times daily, famciclovir 250 mg orally three times daily, or valacyclovir 1 g orally twice daily, all with a duration of 7–10 days. Longer courses could be considered if needed for incomplete healing [7].

Suppressive therapy reduces the frequency of outbreaks by 70–80% and decreases transmission of HSV-2 to noninfected sexual partners. There are several options for suppressive therapy in immunocompetent individuals including acyclovir 400 mg orally twice daily, famciclovir 250 mg orally twice daily, valacyclovir 500 mg orally once daily, or valacyclovir 1 g orally once daily; however, famciclovir may be less effective for the suppression of viral shedding [7]. Additionally, if a patient has 10 or more outbreaks per year, valacyclovir at the 500 mg dosing may be less effective. Because the frequency of outbreaks tends to diminish over time, the provider and patient should consider reevaluating the need for suppressive therapy yearly.

Patients who choose episodic therapy should be instructed to initiate therapy within 24 h of the first lesion or during the outbreak prodrome and given an ample supply of medication for convenient immediate therapy. Patients can take acyclovir 400 mg orally three times daily for 5 days or acyclovir 800 mg orally twice daily for 5 days or acyclovir 800 mg orally three times daily for 2 days or famciclovir 125 mg twice daily for 5 days, famciclovir 1,000 mg orally twice daily for 1 day, famciclovir 500 mg once followed by 250 mg twice daily for 2 days, valacyclovir 500 mg orally twice daily for 3 days, or valacyclovir 1 g orally once daily for 5 days [7].

Rarely, patients develop severe disease which requires hospitalization and parenteral therapy with acyclovir 5–10 mg/kg IV every 8 h for 2–7 days or until clinical improvement is observed. The patient should then continue oral antiviral therapy to complete at least 10 days of total therapy [7].

Pregnancy

Pregnant women infected with herpes risk transmitting infection to the fetus, particularly if primary infection occurs later in pregnancy or active infection is present during labor. If a woman newly contracts genital herpes late in pregnancy, she should be managed in consultation with an infectious disease and maternal-fetal-medicine specialist [7]. Herpes infection requires multiple measures to decrease this risk, as newborn infection can be fatal. Patients with known genital herpes are given antiviral suppressive therapy starting at 36 weeks of gestation and are delivered via cesarean if active lesions or prodromal symptoms are present during labor [20].

Sexual Partners

Sexual partners of patients with HSV should be evaluated and counseled. If sexual partners are asymptomatic, physicians can offer type-specific serologic testing for HSV infection to determine HSV status [7].

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STD Prevention

As a family physician, prevention of sexually transmitted infectious is critical not only through screening, early diagnosis, and treatment of infected patients and their partners but also through primary prevention by addressing behavior change. The family physician must always take a thorough sexual history and provide information on risk reduction in a compassionate and nonjudgmental manner. Patients can reduce risk of infection through abstinence, limiting the number of sexual partners, correct use of barrier methods such as male and female condoms, and vaccination when available. Additional information is available through the curriculum provided by the CDC on STD/HIV National Network of Prevention Training Centers (http://nnptc.org) [7].

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Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

44

Mark Duane Goodman

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Natural History

The illness was first described on June 5, 1981, with the landmark *Morbidity and Mortality Weekly Report* (MMWR) www.cdc.gov/MMWR describing five cases of *Pneumocystis carinii* (now named *Pneumocystis jirovecii*) in Los Angeles, California. It is interesting to note that the MMWR writers note "all the above observations suggest the possibility of a cellular-immune dysfunction related to common exposure that predisposes individuals to opportunistic infections" well before the HIV was identified and named. In 1983, scientists discovered the virus that causes AIDS. The virus was at first named the human T-cell lymphotropic virus type III/lymphadenopathy-associated virus, and this name was later changed to HIV (human immunodeficiency virus). Of the retrovirus family, evidence of infection in humans has now been found as early as the 1920s from human remains and lab specimens in central Africa [1]. Two genetic strains of HIV have been identified, type 1 and type 2. HIV type 1 is the cause of 95% of all infections worldwide.

HIV is spread from person to person through blood, semen, vaginal secretions, and breast milk. Sweat, urine, tears, and saliva are not considered infectious.

Sexual intercourse and needle sharing account for the vast majority of cases, with a smaller number of infants infected at birth or through breast milk. Rare accidental transmission via needle stick or blood exposure remains an occupational hazard as well.

The majority of cases in the United States are from man-to-man (men who have sex with men, MSM) transmission. Worldwide, sexual contact is the most common mode of transmission, though it is thought that parenteral sources such as injection drug use account for about 20% of cases. Risk reduction can be achieved with "safer sex" (barriers or behaviors precluding semen or blood exposure), condom use, clean needles, and universal precautions for healthcare workers.

New data suggests that reduction of an infected person's viral load to an undetectable level renders HIV transmission to theoretically zero, and recently pre-exposure prophylaxis (PrEP) for the prevention of infection of a person at risk (e.g., an uninfected person intimate with an infected partner) has been approved by the US Public Health Service Task Force www.USPHTF Clinical Practice Guidelines 2014. The United States Department of Health and Human Services (HHS) has new initiatives as of November 2019 to improve access and awareness for PrEP under the program named "Ready Set, PrEP" with access to medications at no charge to those without insurance medication benefit [2].

The HIV, upon transmission and breach of host defenses, infects the host CD4 cells (helper/inducer lymphocytes) of the immune system, and by enzymatic insertion into the CD4 replication genome replicates HIV, then destroying the CD4 cell. When enough CD4 cells have been destroyed, host defenses are severely weakened, and eventually the infected person becomes ill developing infections, malnutrition, and malignancies. Without treatment, the average time from infection to the development of an AIDS-defining illness is approximately 10 years, although this interval may vary greatly [3].

Screening and Diagnosis

An estimated 154,000 persons in the United States have HIV infection and are not aware they are infected [4]. In the United States, females, blacks, Hispanic/Latinos, and older individuals are more likely to experience delays in diagnosis. The public health implications of this are enormous: studies demonstrate that patients who are aware of their infection take much more care not to transmit the virus to others [5]. Worldwide, more than 30 million people are infected [6]. More than 75% of all people infected with HIV are in sub-Saharan Africa, and AIDS is the leading

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cause of death for people between the ages of 15 and 59. Also, more than 60% of people living with HIV in low-resource settings are unaware of their status.

HIV Testing

Both patient and the public health are served by HIV discovery, and the newest recommendations by the USPSTF recommend one time screening of all adults from ages 15 to 65 unless they decline (opt out) testing. Pregnant women should be tested as early as possible in each pregnancy, and for those at higher risk, should be tested in the third trimester as well [7]. High-risk individuals, for example, injection drug users, MSM, people who trade sex for money or drugs, and sexual partners of those with HIV, should be tested at least yearly. In addition, testing should be considered in patients presenting with signs of immunodeficiency, weight loss, malignancies, and herpes zoster. In lower-resource settings where there is high prevalence of HIV, the WHO recommends universal screening in clinical settings and community-based screening where possible.

In the United States, direct to consumer in-home HIV testing is available utilizing saliva and is becoming more widely available in other countries [8]. Although the current home-based tests may vary in sensitivity and specificity and lack the option for direct patient counseling and assessment, research suggests that a variety of options for testing and reporting of results is important to remove some of the many barriers that currently exist to testing for the virus [9].

In June of 2014, the Centers for Disease Control and Prevention (CDC) updated testing recommendations, in which laboratories conducting initial testing for HIV should use an FDA-approved antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to screen (a so-called fourth-generation assay). The p24 antigen is typically detectable by 1–2 weeks after transmission of the virus. If that testing is indeterminate, HIV nucleic acid testing (NAT) or quantitative HIV viral load testing is employed. Western blot confirmation is no longer recommended [10].

Symptoms by HIV Stage

Acute HIV Infection

Acute infection represents a burst of viral replication and is marked by fatigue, fever, myalgia, and arthralgia, often with sore throat and swollen lymph nodes. Acute infection resembles acute mononucleosis. Symptoms occur typically 1–4 weeks after transmission and, because of the relatively nonspecific presentation, are often overlooked and the disease goes undiagnosed. At this time, the HIV viral load is very high, but antibodies are typically not yet present, leading to an important diagnostic pearl: if suspected, acute HIV is best confirmed by obtaining HIV RNA (PCR "viral load") testing at this stage. Seroconversion, or the development of positive HIV antibodies, occurs within 4 weeks to 6 months after exposure and very rarely longer than 6 months after exposure.

Asymptomatic HIV Infection

After the acute HIV infection, patients usually enter a period of time lasting 7–10 years with minimal or no symptoms. The viral load declines to a low-level "set point" and the CD4 count slowly declines. The public health is in danger here: an infected person may have no knowledge or symptoms of his/her infection and intimate partners are at risk.

AIDS

The viral load rises, CD4 count drops, symptoms start to appear: at first, rashes "red itchy bump disease" thrush, lymphadenopathy, fatigue, night sweats, weight loss, herpes zoster, recurrent vaginal yeast infections, and unexplained diarrhea are common. When CD4 counts drop below 200 cells/mm^3 (normal range 400–2000 cells/mm^3) or if diagnosed with severe infection or malignancy (candidiasis of lungs or esophagus, invasive cervical cancer, cryptococcosis, cryptosporidiosis, tuberculosis, *Mycobacterium avium*, *Pneumocystis*

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jirovecii, progressive multifocal leukoencephalopathy, salmonella septicemia, toxoplasmosis, cytomegalovirus, chronic or severe herpes simplex, histoplasmosis, isosporiasis, Kaposi's sarcoma, lymphoma, wasting syndrome, or HIV-related encephalopathy), "AIDS" is now diagnosed. While useful in the past in determining severity of disease and for determination of disability, this designation is less useful today, but serves as a reminder of the importance of specific prophylaxis against *Pneumocystis jirovecii*, *Mycobacterium avium*, and toxoplasmosis in persons with advanced immune decline.

Conditions commonly seen in primary care that might raise suspicion for HIV in an individual not thought to be at risk otherwise might include recurrent community-acquired pneumonia, multidermatome herpes zoster or herpes zoster in a young individual, generalized lymphadenopathy, otherwise unexplained peripheral neuropathy, recurrent or severe herpes simplex, or extensive molluscum contagiosum. Patients with persistent fevers or cytopenias of unknown etiology should also be strongly considered for HIV testing.

Medical Management

Pre-exposure Prophylaxis (PrEP)

Both the CDC and the World Health Organization (WHO) recommend the daily use of pre-exposure prophylaxis (PrEP) for those individuals at higher than average risk for acquisition of HIV, along with other methods of risk reduction. This includes groups such as MSM, people in discordant relationships (where only one partner has HIV), and injection drug users at risk. PrEP has been shown to be highly efficacious in preventing virus transmission among those who are adherent to therapy [11]. Currently two Tenofovir products are offered for PrEP protection, with a host of others in the pipeline, including injectable forms. Tenofovir DF with emtricitabine (Truvada) was first approved, followed by Tenofovir Alafenamide with emtricitabine (Descovy) approved in October of 2019.

General guidelines for the use of PrEP include exclusion of acute or chronic HIV infection before beginning therapy, repeating HIV testing at least every 3 months during therapy, obtaining baseline renal function testing, and rechecking renal function at least every 6 months. In Addition, hepatitis status should be checked, as current PrEP therapy would be inadequate treatment and could possibly promote hepatitis resistance or a flare of hepatitis activity. Of note, STI diagnoses are common in PrEP users, and USPHS guidelines recommend STI testing (including triple screening of throat, urethra, and rectum for chlamydia and gonorrhea) at 3 or 6 month intervals for PrEP users [12].

Acute or Suspected Exposure (Post Exposure Prophylaxis [PEP])

In primary care, it is not uncommon to encounter patients who have had an actual or suspected exposure to HIV. These exposures may be encountered in an occupational environment (such as a needle stick) or otherwise be potentially exposed through body fluid contact such as may occur with unprotected sex, sexual assault, or the use of shared needles or injection equipment. Levels of risk for transmission are variable and in the United States can be assessed by calling the National Clinician's Post Exposure Prophylaxis Hotline 24 h a day at 888-448-4911. While post exposure prophylaxis is generally safe, toxicity, sometimes severe, can occur which may include toxic epidermal necrolysis and severe hepatitis. Therefore, it is important to weigh the risks and benefits of post exposure prophylaxis with each patient. Also, in cases where prophylaxis is unsuccessful, the selection of resistant strains of HIV may make treating the infection problematic. Therefore, PEP use should be avoided in people who have ongoing or repeated HIV exposures [13].

Post exposure prophylaxis should be started within 72 h of exposure and continued for 28 days. Optimally, a three-drug regimen is chosen to take into account factors such as efficacy, pill burden, and dosing frequency as well as cost. CDC and WHO recommendations are for three drugs, although WHO also states that two-drug regimens, while not optimal, are acceptable [14].

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Evaluation of Patients with HIV

After diagnosis and upon entry into care, every patient should have: a complete medical history, physical examination, and laboratory evaluation, along with counsel about transmission, self-care, intimate partner care, and the public health. A baseline evaluation, as recommended by the Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, includes HIV antibody testing; CD4 T-cell count; plasma HIV RNA (viral load); CBC; chemistry profile; transaminase levels; BUN/Cr; urinalysis; serology for hepatitis A, B, and C viruses; glucose; lipids; and HIV genotypic resistance testing. In addition, some authorities recommend HLA-B 5701 to screen for abacavir sensitivity; a tropism test (for future consideration of a CCR5 antagonist); chlamydia, gonorrhea, and syphilis testing; PPD/QuantiFERON/chest X-ray testing for TB (a PPD is considered positive for those living with HIV when induration measures 5 mm rather than the usual 10 mm); toxoplasmosis antibody testing; CMV and varicella serology; cervical pap smear (at 6-month intervals initially, then yearly after two negative smears); and an anal/rectal pap smear (to screen for HPV-related squamous cell carcinoma of the anus) [15] (Table 1).

Pregnancy testing is important for women of child-bearing age, along with a discussion of contraception and avoidance of HIV treatment regimens that may be teratogenic [16].

A patient-centered multidisciplinary approach is often necessary: HIV is a complex illness with enormous emotional and physical implications. Patients still fear job loss, insurance and medical cost, shunning and isolation, along with the fears surrounding illness and death or a foreshortened life. Coinfections, substance use, housing concerns, and mental illness may also be present, and patients often are best served by a team and sometimes an advocate. Family physicians can be the advocate and team leader: continuity of care is good medicine against the fear of abandonment and shunning, and comprehensive care is critical to long-term health.

Immunizations include annual influenza vaccination, pneumococcal vaccination, hepatitis A and B vaccination for those who are vulnerable, latent or active TB treatment, and treatment for hepatitis B and/or C for those found to be coinfected. Meningococcal vaccine is also recommended. Live vaccinations are generally contraindicated: these include oral poliomyelitis, herpes zoster, varicella, measles, mumps, and rubella (at least until the immune system is restored). Human papillomavirus (HPV) vaccination, though not studied in persons living with HIV, is recommended and now has an expanded age range, from age 9, and can be given in some circumstances to age 45 [17].

The CD4 count and HIV viral load are repeated at 1 month after initiation of highly active antiretroviral therapy (HAART), after therapy changes, then at 3–6 months, and later annually at follow-up visits for those found to have achieved:

- A consistently suppressed viral load (ideally fewer than 20 copies or "undetectable")
- A stable protective CD4 count (more than 300 cells/mm^3)
- No active illnesses

HAART

Despite the very rare suggestion of "cures" in the past, and two documented cases of cure after marrow eradication and stem cell transplant, control of HIV is the goal for now [18]. Very quickly after medical suppression of viral replication ceases, most patients experience a rapid return of detectable and increasing viral loads, then the inevitable destruction of CD4 cells and return to illness. Viral reservoirs are postulated, perhaps in the central nervous system, spleen, or marrow, that permit the virus to remain in dormancy during treatment, only to rapidly reappear "when the coast is clear."

The CDC now recommends that ALL patients infected with HIV, independent of viral load or CD4 count at diagnosis, are treated with highly active antiretroviral therapy (HAART), with the goal being an undetectable viral load and normal range CD4 count. Linkage into care and

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Table 1 Testing for HIV-positive patients

Test	Frequency
HIV serology – confirmatory	Initial visit
CD4 count	Initially, then at 3–6 months. If stable (see text) once yearly
Viral load	Initially, then every 3 months when on treatment. If stable (see text) once yearly
HIV resistance genotype	Initially and after treatment failure prior to change in treatment regimen
Complete blood count	Initially, then every 3–6 months
Lipid panel and serum glucose	Initially, then every 3–6 months
Chemistry panel	Initial visit, then every 6–12 months
Toxoplasma serology	Initially and if CD4 falls below 100 cells/mm^3
CMV and VZV serology	Initial visit
Syphilis serology	Initially, then yearly
Chlamydia and gonorrhea urine NAAT	Initially and every 3 months to yearly depending on risk
G-6-PD screening	Initial visit
PPD	Initially, then yearly if negative
Hepatitis serologies (A, B, and C)	Initial visit
Pap smear	Initially in 6 months and yearly if negative *x*2
HLA-B∗5701	If consideration is being given to the use of abacavir
Co-receptor tropism assay	If consideration is being given to the use of a CCR5 antagonist

adherence to medications can be difficult and uneven, but clarification of treatment regimens and once-daily combination medications provide some promise for achieving this goal. Medications break viral replication through the use of replication enzyme inhibitors. The classes include:

- Nucleoside reverse transcriptase inhibitors (e.g., zidovudine, lamivudine)
- Protease inhibitors (e.g., tipranavir, ritonavir)
- Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine)
- Integrase strand transfer inhibitors (e.g., raltegravir, dolutegravir)
- Fusion inhibitors (enfuvirtide)
- CCR5 antagonists (maraviroc)

Fixed dose once-daily combination products are currently available. All treatment recommendations include medications from more than one enzyme group, to provide added protection against development of viral resistance and resurgence. Novel treatments include fixed dose combinations including only two antiretroviral classes: efficacy studies support these choices for some patients (dolutegravir/rilpivirine and dolutegravir/lamivudine) [19]. In addition, monthly injectable cabotegravir/rilpivirine holds promise as another opportunity for treatment [20]. Full treatment guidelines can be found at www.aidsinfo.nih.gov/guidelines and telephone guidance from the National HIV Consultation Service of the Department of Family and Community Medicine at San Francisco General Hospital at (800):933–3413.

Generic medication is now available in some of the enzyme inhibitor classes, costs are becoming more approachable, and AIDS Drug Assistance Programs (ADAP or Ryan White programs) and manufacturer patient assistance programs can help to provide medication access. Clinical research trials may appeal to some, and monitoring and medications are provided for those who consent to participate.

CD4 count monitoring and HIV viral loads after treatment has begun may suggest nonadherence or the development of resistance. If a formerly undetectable viral load begins to rise and then becomes undetectable again, viral emergence from reservoirs may be to blame or a period of nonadherence may be the cause. Protracted and

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continuing viral load elevation suggests nonadherence or the development of viral resistance, repeating a genotype resistance assay and switching to a different HAART regimen, is in order, along with a determination of the cause of nonadherence if possible, and a remedy. Despite the enormous risk of nonadherence, daily lifetime treatment is difficult and easily sabotaged. Depression, substance use, relationship stresses, homelessness, mental illness, transportation, insurance, and medication access can make adherence difficult for patients and medical caregivers alike.

Management of the Immunocompromised Patient

Prophylaxis

If the CD4 counts fall below 200 cells/mm^3, prophylaxis against *Pneumocystis jirovecii* (also abbreviated as PCP, referring to the former name of *Pneumocystis carinii*) with daily trimethoprim-sulfamethoxazole (TMP-SMX 1 DS tab daily) is recommended. For the sulfa allergic, dapsone and pentamidine can be considered. TMP-SMX has the added benefit for prophylaxis against toxoplasmosis. Below a count of 50 CD4 lymphocytes/mm^3, azithromycin is recommended for prophylaxis against *Mycobacterium avium* complex (MAC).

HIV Wasting and Fatigue

Muscle loss, weight loss, fatigue, and fevers/night sweats commonly affect those living with HIV. Causes can include sepsis, infection, malignancy, malnutrition, malabsorption, vitamin D deficiency, and low testosterone. Thorough investigation including cultures, imaging, and lab work is required. Lipodystrophy, with adipose abdomens, and "buffalo hump," with facial wasting and lower extremity wasting is a hallmark of HIV and in some cases may be caused by antiretroviral therapy [21].

Skin and Mucosa

Often the first signs of HIV are evident on the skin. From common "red itchy bump disease" seborrhea, candida, and intertrigo to malignancies such as basal cell skin cancers, squamous cell cancers, melanomas, and Kaposi's sarcoma, aggressive culture, consultation, and biopsy are wise. Rapid expansion of molluscum contagiosum reflects declining immune defenses, as does the appearance of varicella zoster. Onychomycosis of finger and toenails may also be seen [22]. More commonly cellulitis, MRSA skin infections, felons, herpes infections, and hairy leukoplakia may make an appearance.

Eyes

In patients with CD4 counts of less than 50–100 cells/μL, 6–12 monthly ophthalmology exams are recommended by a provider skilled in HIV eye manifestations, which may include cytomegalovirus infection and risk of blindness [23].

Pulmonary

From the beginning of awareness about HIV, lungs have been an early and frequent host to disease. Tuberculosis treatment is a major and worrisome worldwide focus of HIV care. Pneumocystis heralds immune decline, and the lungs can also be host to Kaposi's sarcoma, Mycobacterium avium (and others), and numerous other forms of pneumonia. Pneumocystis usually requires bronchoscopy for definitive diagnosis, but is inferred by the characteristic pattern on chest X-ray ("snowstorm" infiltrate) insidious dyspnea, and elevated LDH. In the age of HAART, it is increasingly recognized that conditions such as COPD, lung cancer, pulmonary hypertension, and bacterial lung infections may be increased among patients living with HIV [24].

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Cardiac

With the advances in HIV care, patients are living longer, increasing their likelihood of cardiac disease. Many antiretroviral medications cause lipid disorders: along with tobacco use, viral cardiomyopathies, and inflammatory effects, cardiac disease has become a major threat to long-term health in this population [25].

Blood and Lymph

Lymphoma is one of the AIDS diagnostic illnesses and is seen in a high proportion of persons with advanced HIV disease. Anemia from medication, malnutrition, or toxicity to marrow is common (note that macrocytosis can be a surrogate marker of adherence, appearing as a side effect of zidovudine therapy). Thrombocytopenia and leukopenia commonly occur, perhaps as a direct effect of HIV infection, but requiring investigation as to their cause. Generalized lymph node enlargement is often evident in early HIV infection and may persist throughout the course of illness. Differential diagnosis of lymphadenopathy includes malignancy, infection, and reactive changes [26].

GI Tract and Liver

Lactic acidosis can result from antiretroviral treatment for HIV, presenting as fatigue, myalgia, nausea, and abdominal pain [27]. Pancreatitis is seen frequently in patients with HIV, both due to the infection and as a side effect of treatment [28]. Coinfection with hepatitis B and/or C infection requires coordinated management and, often, consultation. The liver is subject to inflammation as a side effect of antiretroviral therapy and infection from mycobacteria, fungi, and malignancy.

Renal

Renal impairment is an emerging concern, in large measure because of the nephrotoxicity of some HIV medications. Nonsteroidal anti-inflammatories can be problematic, along with the effects of hypertension, diabetes, and some antibiotic therapies. Specialized centers have now begun kidney transplantation in some cases of persons living with HIV and advanced kidney disease [29].

Musculoskeletal

Both HIV and antiretroviral treatment are thought to contribute to higher rates of osteopenia in patients living with HIV. Some authorities recommend screening for osteopenia in all males with HIV over 50, all postmenopausal women with HIV, and all patients with suspected fragility fractures [30]. Avascular necrosis of bone is not uncommonly seen [31].

Neurologic System/CNS

Central nervous system disorders can include Toxoplasmosis, Cryptococcus, CNS lymphoma, and progressive multifocal leukoencephalopathy (JC virus). AIDS dementia is a major concern, presumably from direct HIV infection of the brain. This manifests as impaired decision-making, forgetfulness, confusion, and motor disorders. Both PML and AIDS dementia have some reversal potentially with HAART [32].

HIV in Children

The number of HIV-infected children in the United States declined by two-thirds from 1992 to 1997 according to the CDC. In one of the great public health interventions of our times, and based upon the landmark study in 1994 by the Pediatric AIDS Clinical Trials Group (ACTG 076), zidovudine (AZT) given to HIV-infected women in the second or third trimester and continued during labor remarkably reduced rates of perinatal transmission of HIV. Further updates reducing maternal-infant transmission (MIT) have refined this to even lower levels of transmission [33]. In high-income countries, mothers should abstain from breastfeeding and instead provide formula, as HIV may be transmitted to their infants in up to 40% of cases. In low-

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and some middle-income countries, where the health risks of waterborne disease and costs of formula are prohibitive, exclusive breastfeeding for the first 6 months of life is recommended by the WHO and UNICEF [34].

All pregnant women should be screened for HIV as early as possible in each pregnancy. Women with HIV who take antiretroviral medication during pregnancy as recommended can reduce the risk of transmitting HIV to their babies to less than 1%. HIV disproportionately affects African American babies in the United States. Cesarean delivery is indicated if maternal HIV viral load is >1000 copies/mm^3 of blood. HIV may also be transmitted through breast milk, creating concern in those parts of the world where safe and reliable alternatives to breastfeeding may not exist. Small numbers of children have been infected through contaminated blood or blood products prior to screening of the blood supply in 1985 and through sexual or physical abuse by HIV-infected adults.

HIV infection is often difficult to diagnose in infants and children: symptoms may not be present, and antibodies present in the child's blood may be maternal in origin for the first 18 months. HIV PCR/viral load testing on an infant or child is more reliable, and serial testing may be indicated.

Signs and symptoms may include failure to thrive, delayed developmental milestones, neurologic complications, frequent infections, severe and recurrent candida infections, and respiratory infections. In low-resourced parts of the world, AIDS orphans are a grim reminder of the impact of HIV infection on families and communities [35].

Treatment protocols for children and infants, using liquid formulations and weight-based dosing, can be found at www.aidsinfo.nih.gov/pediatricguidelines.

HIV in Women

Greater challenges may exist for women living with HIV: caring for family, access to medical care and treatment, social stigma, and gender-specific concerns are identified. Early research tended to exclude women from clinical trials, so less is known. HIV can cause higher incidence of cervical dysplasia, invasive cervical cancer, recurrent herpes infections, yeast infections, and HPV. More frequent pap screening is recommended, and support systems and advocacy are recognized as needs in many communities. Minority women are disproportionally affected by HIV, and for some, employment, insurance, and responsibilities of children create unique challenges [36].

HIV and Aging

About half of older people with HIV have been infected for 1 year or less. The rates of HIV in patients older than 50 years are 12 times higher for African Americans and 5 times higher for Hispanics compared with whites. Older people may be at risk because healthcare providers may not test for HIV in older folks, older people may lack awareness of their risk, many older people are newly single, and many have limited knowledge about safer sex. Of interest, older patients are found to have better medication adherence to HAART and respond well to antiretroviral treatment. Some illnesses impacted by aging patients living with HIV include dementia, depression, diabetes, hyperlipidemia, cardiac disease, infection, and medication interactions. Social isolation and stigma can be difficult in older adults, contributing to depression, substance use, and increased mortality [37].

Summary of HIV for Family Physicians

Though complex, our role is vitally important, with immense satisfaction in both the individual relationships with our patients affected with HIV and in the health of our communities. The whole person care delivered for persons living with HIV in family medicine offices and patient-centered medical homes can help earn trust, which is vital for adherence and long-term health. In addition, many family physicians care for "people at the margins" the homeless, incarcerated, transgender, migrants, and patients living in rural areas: each

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requires dexterity in order to achieve care goals and to support trust building.

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Bacteremia and Sepsis

45

Omofolarin B. Fasuyi and Folashade S. Omole

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General Principles

Public Health and Economic Burden

Sepsis remains the primary cause of death from infection despite advances in vaccines, antibiotics, and acute care [1]. It is estimated to affect over 30 million people annually worldwide of which more than five million die [2, 3]. Although the majority of sepsis cases and sepsis related deaths are estimated to occur in low and middle-income countries, its impact remains significant globally transcending geographical location and socioeconomic status [4]. For instance, in the United States (US), sepsis affects over one million people and accounts for approximately 270,000 deaths annually [3, 5].

Sepsis treatment uses significant resources globally. The median of the mean hospital-wide cost of sepsis per patient is estimated at $32,421 [3]. In USA, sepsis is the most common cause of in-hospital deaths and costs more than $24 billion annually [6]. The economic burden of sepsis and its overall impact on morbidity and mortality as well as health and well-being of affected patients and their families is significant [7]. Fortunately,

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timely targeted interventions improve outcomes in sepsis [1, 5, 6]. Prompt interventions at access points into the health care system play a crucial role in mitigating the negative outcomes of sepsis. It is likely that patients will present to ambulatory settings (primary care physician office, urgent care facility, etc.) earlier in the course of their infection. This underscores the importance of increased family physician awareness of sepsis and sepsis-related issues.

Definitions and Classification

Bacteremia is the presence of viable bacteria in circulating blood. Bacteremia is usually associated with a symptomatic infection and is demonstrable by bacterial growth from an aseptically collected blood culture specimen [8]. However, bacteremia often occurs transiently without any clinical consequences.

Sepsis was previously defined as a known or suspected infection with systemic manifestations of infection [9]. Most of the manifestations previously required to diagnose sepsis are no longer necessary for diagnosis [1, 5]. The most recent definitions were revised in 2016. The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) concluded that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection rather than increasingly severe manifestations of uncontrolled bacterial infection **[**1**,** 10**]**.

Septic shock was previously defined as sepsis-induced hypotension not responsive to adequate fluid resuscitation[11]. The 2016 task force revision now defines septic shock as sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) $\geq$65 mm Hg and having a serum lactate level $>$2 mmol/L (18 mg/dL) despite adequate volume resuscitation [1, 12]. Patients in this subset of sepsis have particularly profound circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than with sepsis alone [1]. Septic shock is associated with hospital mortality rates as high as 80% [13].

Approach to the Patient

Clinical presentation: Early identification and appropriate evidence-based medical care are key to increasing the chance of survival and improving overall outcomes in sepsis [1, 5–7, 14]. An aging population with more chronic illnesses, greater use of invasive procedures, immunosuppressive drugs, chemotherapy, transplantation, and increasing microbial resistance to antibiotics all contribute to increasing rates of sepsis. Bacterial (mainly gram-positive) infection is the most common cause of sepsis. Sepsis from fungal, viral, or parasitic infections can occur [5, 15]. The case-fatality rate of sepsis depends on the setting, microbe, and severity of disease. Mortality can be as high as 30% for sepsis and 80% for septic shock [13].

The most common sites of infection are the respiratory, genitourinary, and gastrointestinal systems, as well as the skin and soft tissue [16]. These sites account for over 80% of all cases of sepsis [17]. Fever is often the first obvious manifestation of sepsis [16]. However, biological and clinical heterogeneity in affected individuals such as age, baseline medical status, concurrent injuries (including surgery), medications, anatomical source and type of infecting organism add to the complexity of manifestations as well as the resultant morbidity severity and mortality [1, 18]. Therefore, clinical suspicion is key to an appropriate and timely diagnosis. In the elderly, for example, anorexia, withdrawal, agitation, disorientation, and confusion may be early signs of sepsis [16, 19]. In neonates, exaggerated physiologic jaundice, tachypnea, poor feeding, and reduced tone may be the only manifestations of sepsis.

History taking focused on the chief complaint with a pertinent review of systems is often adequate for initial triage. However, some patient with sepsis may present with nonspecific constitutional symptoms.

Physical Examination A complete physical examination is indicated. This is important because sepsis from an infection in less obvious areas such as the pelvis or perineum may occur. However, a thorough physical examination

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should not delay early initiation of life-saving care.

Diagnosis

The **Sequential [Sepsis-related] Organ Failure Assessment (SOFA)** score (Table 1) is currently the main tool used to assess sepsis associated organ dysfunction. An advantage of SOFA is that it grades abnormality by organ system and accounts for clinical interventions. SOFA can be scored retrospectively (either manually or by automated systems) from clinical and laboratory measures often performed routinely as part of acute patient management [1]. SOFA is helpful in sequential assessment of the severity of organ dysfunction in patients who are critically ill from sepsis. It uses measurements of major organ function to calculate a severity score [20]. SOFA calculators are freely available online and they can be readily utilized for patient care wherever there is internet access.

Organ dysfunction can be identified as an acute change in total SOFA score $\geq$2 points consequent to the infection. Of the sequentially calculated scores, the mean and the highest SOFA scores are most predictive of mortality. Scores that increase by about 30% are associated with a mortality of at least 50% [21].

Parameters that are used in calculating the SOFA severity score are as listed below [20, 22].

- Ratio of arterial oxygen tension to the fraction of inspired oxygen (PaO_2/FiO_2)
- The mean arterial pressure or the amount of vasopressor medication necessary to achieve or maintain optimal mean arterial pressure (MAP)
- Bilirubin level
- Platelet concentration
- Glasgow coma score
- Serum creatinine level or urine output

QuickSOFA (qSOFA) is a bedside clinical score that helps with rapid identification of patients that are more likely to have poor outcomes. It can be used in ambulatory, emergency, or non-ICU in-patient settings [1, 10]. The presence of at least 2 qSOFA clinical criteria (Table 2) predicts poor outcomes [24].

The qSOFA is however statistically inferior compared with SOFA for encounters in the ICU and has a statistically lower content validity as a measure of multiorgan dysfunction. Thus, the task force recommended use of a SOFA score of 2 points or more in encounters with infection as criteria for sepsis and use of qSOFA in non-ICU settings to consider the possibility of sepsis [1, 25, 26].

Laboratory Workup and Imaging

There is no gold standard diagnostic test for sepsis [10], rather sepsis is a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection [1]. Additionally, although bacterial infections are the most common cause of sepsis, viral, fungal, or parasitic infections are also known causes of sepsis.

Routine laboratory workup for sepsis includes two sets of blood cultures (drawn before starting antibiotics if possible). Urinalysis, lactate level, complete blood count (CBC), comprehensive metabolic panel (CMP), clotting profile, urine culture, and cultures from other suspected sites (wound, respiratory secretions, CSF, or other body fluids) are important as well. Other laboratory tests and imaging studies should be individualized based on history and physical examination findings.

Lactate levels have been strongly correlated with morbidity and mortality [27, 28]. Lactate level is an independent prognostic predictor of mortality for patients with sepsis. It has superior discriminative power to qSOFA and shows discriminative ability similar to that of SOFA [29].

Differential Diagnosis

Various conditions can mimic sepsis. Although the differential is very broad, common causes of systemic inflammatory response syndrome

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Table 1 [23] Sequential Organ Failure Assessment (SOFA) score

Respiratory system	
PaO_2/FiO_2 (mmHg)	SOFA score
> 400	0
< 400	1
< 300	2
< 200 with respiratory support	3
< 100 with respiratory support	4
Nervous system	
Glasgow Coma Scale	SOFA score
15	0
13–14	1
10–12	2
6–9	3
< 6	4
Cardiovascular system	
Mean arterial pressure (MAP) OR administration of vasopressors required	SOFA score
MAP > 70 mmHg	0
MAP < 70 mm/Hg	1
Dopamine ≤ 5 μg/kg/min or dobutamine (any dose)	2
Dopamine > 5 μg/kg/min OR epinephrine ≤ 0.1 μg/kg/min OR norepinephrine ≤ 0.1 μg/kg/min	3
Dopamine > 15 μh/kg/min OR epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min	4
Liver	
Bilirubin (mg/dl) [μmol/L]	SOFA score
< 1.2 (< 20)	0
1.2–1.9 [20–32]	1
2.0–5.9 [33–101]	2
6.0–11.9 [102–204]	3
> 12.0 [> 204]	4
Coagulation	
Platelets ×103/ml	SOFA score
> 150	0
< 150	1
< 100	2
< 50	3
< 20	4
Kidneys	
Creatinine (mg/dl) [μmol/L]; urine output	SOFA score
< 1.2 [< 110]	0
1.2–1.9 [110–170]	1
2.0–3.4 [171–299]	2
3.5–4.9 [300–440] (or urine output < 500 ml/day)	3
> 5.0 [> 440]; urine output < 200 ml/day	4

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(SIRS) listed below are differential diagnoses of sepsis.

Systemic inflammatory response syndrome (SIRS) is a condition in which an uncontrolled inflammatory response occurs in response to an insult. It can occur even in the absence of probable or documented infection [1, 5, 30, 31]. They may simply reflect an appropriate host response. SIRS may present in a range of conditions (see list below) in many hospitalized patients including

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Table 2 Quick Sequential Organ Failure Assessment (qSOFA) score

Quick SOFA (qSOFA) criteria:	Score
Respiratory rate of ≥22/min	1
Altered mental status (GCS <15)	1
Systolic blood pressure ≤ 100 mm Hg	1

those who never develop infection and never incur adverse outcomes [1, 30].

Some causes of systemic inflammatory response syndrome (SIRS) [31]:

- Anaphylaxis
- Sterile inflammation, for example, vasculitis, acute pancreatitis
- Hypovolemia, for example, acute blood loss
- Trauma
- Respiratory diseases, for example, in acute respiratory failure, chemical aspiration
- Ischemia, for example, in acute myocardial infarction, acute mesenteric ischemia
- Diabetic ketoacidosis
- Adrenal insufficiency
- Transfusion reaction
- Burns
- Autoimmune disorder
- Substance abuse or intoxication
- Drug overdose
- Inborn errors of metabolism

In the face of manifestations of SIRS, exclusion of sepsis is often a challenge as microbiological investigations are often negative for various reasons. These include antibiotic administration prior to sample collection, or technical issues related to blood culture. Only 30–50% of patients diagnosed with sepsis have positive blood cultures [2]. Negative or inconclusive blood cultures do not exclude the possibility of sepsis in patients when there is a high index of suspicion of this condition. Thus, in the clinical setting, the diagnosis of sepsis is often empirical or made retrospectively.

Treatment

Aggressive and timely management of patients with sepsis is paramount. Expeditious transfer to an inpatient setting should occur. Sepsis should generally warrant greater levels of monitoring and intervention, including possible admission to critical care or high-dependency facility [1]. Intravenous fluid resuscitation can be started in the ambulatory setting. Blood culture collection should not cause delay in necessary care at any point. Empiric antibiotics should be started after blood culture sample collection and in any case within 1 h of arrival at the hospital or emergency room. The antibiotic choice can be based on the patient's history (e.g., recent antibiotics used), clinical context (community vs. health setting-acquired infection), most likely pathogens, local susceptibility patterns, and cost-effectiveness. Fluid resuscitation should be initiated and continued upon arrival to the emergency room or hospital. If septic shock is present, vasopressor therapy should be initiated.

If a localized source of infection is detected, intervention (such as abscess drainage) should be undertaken as soon as possible within the first 12 h after the diagnosis is made [9].

The Surviving Sepsis Campaign (SSC) care bundle (see list below) is a selected set of elements of care distilled from evidence-based practice guidelines. Using the bundle simplifies complex processes of care of patients with severe sepsis and has demonstrated marked improvements in survival rates after sepsis [9, 32, 33].

Hour-1 Surviving Sepsis Campaign Bundle of Care is to be completed within 1 h from time zero. "Time zero" or "time of presentation" is defined as the time of triage in the emergency department or, if referred from another care location, from the earliest chart annotation consistent with all elements of sepsis or septic shock ascertained through chart review [33].

Hour-1 Surviving Sepsis Campaign care bundles components are listed below [33]

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics

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4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mmHg

Prevention

Infection prevention efforts, including those targeting both community-acquired and healthcare-associated infections, can reduce sepsis incidence [34, 35]. Intentional public health education efforts to raise public and clinician awareness of sepsis and its sequelae will likely help with prevention, early diagnosis, and prompt interventions. Patients at increased risk of sepsis should be appropriately vaccinated against pneumococci, *Haemophilus influenzae* type b, meningococci, and the influenza virus. The Centers for Disease Control (CDC) strategies for preventing infections include promotion of vaccination for diseases like pneumococcus and meningitis, smoking cessation programs to prevent community-acquired pneumonia, and strategies to prevent healthcare-associated infections. Early identification and appropriate treatment of infection in all patients especially those at increased risk of sepsis reduces chances of progression to bacteremia and sepsis. Good nutrition and lifestyle choices (including regular exercise) boost the body's natural defense system and ability to fight infection. Hand hygiene and good general hygiene practices reduce the rate of infection transmission. Antibiotic stewardship reduces the prevalence of bacterial resistance in the community.

Family and Community Issues

Sepsis survivorship is a substantial and underrecognized public health problem with major implications for patients, families, and the healthcare system. Sepsis survivors often develop physical, cognitive, and affective deficits in the months and years after discharge. These new deficits are relatively more severe among patients who were in good health prior to hospitalization for sepsis [36]. Declines in the level of functioning impact many areas of a patient's life ranging from the ability to perform activities of daily living (ADL) to executive functioning [7, 37]. This may affect the structure and functioning of the family unit. Additional issues include caregiver fatigue, marital stress, and other psychosocial, medical, economic, and legal issues. It is important for family physicians to maintain vigilance for possible sequelae of sepsis among patients and their families beginning at the discharge planning phase of care. An understanding of immediate and long-term outcomes helps with managing expectations and setting goals of care especially when assessing options for short- or long-term care.

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Selected Infectious Diseases

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Toxoplasmosis

Toxoplasmosis is an infection with a worldwide distribution, affecting immunocompetent and immunodeficient hosts, as well as pregnant women and newborn babies.

Etiology and Epidemiology

Toxoplasma gondii is an extremely successful protozoal parasite, which infects almost all mammalian species including humans. Approximately 30% of the human population is chronically infected with *T. gondii.* The severity of congenital infection is inversely proportional to gestational age at the time of infection. The transmission rate to the fetus is 10–15% in the first trimester, 22–40% in the second, and 68% in the third trimester [1].

Toxoplasma gondii exists in four different stages: oocyst, which is the product of the parasite cycle in the cat's intestine. Subsequently, they are excreted in cat feces. In the soil, they transform into the infectious form, the tachyzoite, which penetrates all nucleated cells and replicates rapidly, causing tissue destruction. This stage is responsible for the clinical manifestation of the disease. The body's immune response transforms these tachyzoites into slowly replicating bradyzoites. This tissue cyst can be found in the brain, heart, and skeletal muscle.

A single cat can pass more than 100 million nonsporulated oocysts, which become infective within 1–5 days after defecation. Freezing, chemical, or physical treatment (such as chlorine or ozone treatment) does not destroy sporulated oocysts; only heating >55 °C reliably destroys them [2].

There are four means of acquiring toxoplasmosis in humans: ingestion of infectious oocysts from the environment (soil contaminated with feline feces), ingestion of tissue cysts from an infected animal, contaminated fruits/vegetables, and contaminated water. Vertical transmission from an infected mother to her fetus is possible. The final route of acquisition is via blood transfusion or solid organ transplantation from an infected donor [3].

Ingestion of raw or undercooked food (including beef, goat, lamb, or pork) or drinking unpasteurized goat milk is responsible for the majority of toxoplasmosis cases in the USA and Europe. In other parts of the world, infection with toxoplasma is more likely due to environmental exposure. Once an individual is infected, the

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organism lies dormant in eye, muscle, or brain tissue and is not eliminated [4].

Clinical Features

Toxoplasma infections are divided into four categories: toxoplasmosis in the immunocompetent host, toxoplasmosis in the immunocompromised host, toxoplasmosis in pregnancy, and congenital toxoplasmosis.

Acquired Toxoplasmosis Infection in the Immunocompetent Host: Infection in this group is asymptomatic in 80–90% of patients. On the other hand, if symptoms develop, the most common manifestation is bilateral, symmetric cervical adenopathy. Associated symptoms are fever, chills, sweat, headaches, myalgia, pharyngitis, hepatomegaly, and splenomegaly (mononucleosis-like symptoms). This is a benign self-limiting course and may last from a few weeks to months. Acute toxoplasmosis may be mistaken for acute Epstein-Barr virus (EBV) or as *Cytomegalovirus* infection (CMV), especially since atypical lymphocytes can be seen in toxoplasmosis infection. There is an association between *T. gondii* and mental health illness, mostly schizophrenia and generalized anxiety disorder [5, 6, 7]. Human immunodeficiency virus (HIV) also should be included as part of the initial evaluation. Other differential diagnoses might include syphilis, sarcoidosis, Hodgkin's disease, and lymphomas.

Toxoplasma gondii has the ability to disseminate through the bloodstream and can cross vascular barriers such as the ocular area, causing ocular toxoplasmosis (posterior uveitis or necrotizing retinochoroiditis). These lesions commonly "heal" within 2–4 months after infection, leaving a hyperpigmented scar, a result of retinal pigment epithelium disruption. Acute retinal lesions may be associated with adjacent old scars indicating recurrent attacks.

Toxoplasmosis Infection in the Immunocompromised Host: In immunocompromised individuals, especially patients with acquired immunodeficiency syndrome (AIDS), usually when the CD4 lymphocyte count is below 100 cells/microL, the parasite can reactivate and cause disease. All patients with HIV should be screened for *Toxoplasma gondii* infection. The most common site of reactivation is the central nervous system (CNS), and the next is the retina. Toxoplasma infection is the most common CNS opportunistic infection in AIDS patients.

Cerebral Toxoplasmosis: Cerebral toxoplasmosis usually presents with clinical symptomatology such as fever, neurological deficit, confusion, and headaches. Laboratory evaluation includes serologic evaluation with immunoglobulin G (IgG). The majority of patients with cerebral toxoplasmosis are positive for IgG antibodies. Radiologic evaluation includes brain imaging (CT or MRI). Ring-enhancing brain lesions are often associated with edema, with predilection for the basal ganglia. While brain biopsy is the definitive test to confirm the infection, the morbidity associated with this procedure means that the diagnosis is usually made on the basis of the clinical picture, serology, and imaging findings. Cerebrospinal fluid (CSF) may demonstrate elevated protein and mononuclear pleocytosis. The differential diagnosis includes CNS lymphoma, cryptococcosis, mycobacterial infection, or bacterial abscess.

Chorioretinitis: Chorioretinitis usually presents with eye pain and visual deficit. An ophthalmologic evaluation reveals posterior uveitis, retinal lesions, and vitreous inflammation.

Toxoplasmosis in Pregnancy: Women of childbearing age may acquire toxoplasmosis, resulting in primary maternal infection. Fetal infection may occur from transmission of the parasite from mother to fetus before the development of a protective immunologic response in the mother.

During acute infection, the mother is usually asymptomatic, but when symptoms develop, they are vague: fever, malaise, myalgia, fatigue, and headaches. Lymphadenopathy is usually present. Pregnant women who have mono-like symptoms but are EBV serology negative should be tested for toxoplasmosis, cytomegalovirus, and, if at risk, for HIV.

Infections during pregnancy are most reliably diagnosed by blood samples at least 2 weeks apart using toxoplasma-specific IgG or IgM. A maternal primary toxoplasma infection poses serious

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risk to the fetus, but a reactivation of primary toxoplasmosis does not (congenital toxoplasmosis secondary to reinfection is rare). The majority of fetuses exposed to acute toxoplasmosis infection in the first trimester die in utero or develop severe neurological or ophthalmological sequelae. Fetuses infected in the second or third trimester tend to develop milder or subclinical findings at birth.

Congenital Toxoplasmosis: Neonates with congenitally acquired toxoplasmosis may have few, if any, manifestations on their physical exams and remain asymptomatic. The classic triad of intracranial calcifications, hydrocephalus, and chorioretinitis occurs in few of the infected newborns. If there is a high index of suspicion, then laboratory and radiologic evaluations are needed to diagnose congenital toxoplasmosis – ophthalmologic evaluation, seeking retinal scarring (focal necrotizing retinitis). CSF shows pleocytosis with mononuclear cells and elevated protein. Toxoplasma-specific IgM or isolation of *T. gondii* from the CSF can be attempted. Ultrasound of the head may reveal calcifications in brain parenchyma, but head CT is more sensitive in visualizing these lesions.

Differential diagnosis in the neonatal period includes other congenitally acquired diseases that include rubella, CMV, syphilis, and herpes infection.

Laboratory Diagnosis

The use of serologic tests to search for anti-*Toxoplasma gondii* is a primary method of diagnosis. The tests most commonly used in routine laboratories for the detection of anti-*Toxoplasma gondii* IgG are the double sandwich enzyme-linked immunosorbent assay (ELISA), the indirect fluorescent-antibody assay (IFA), the indirect hemagglutination assay, and the direct agglutination test and for anti- *Toxoplasma gondii* IgM, double sandwich ELISA, immunosorbent agglutination assay (ISAGA), and IFA.

The Toxoplasma Serology Laboratory at the Palo Alto Medical Foundation (USA) www.pamf.org/serology/clinicianguide.html offers advice to clinicians about ordering and interpretation of test.

IgG antibodies: usually appear between 1 and 2 weeks after acquiring the infection, peak within 1–2 months, and usually persist for life. A positive test confirms that an infection has occurred but does not indicate how long ago occurred. A number of tests looking for "avidity" to toxoplasma IgG antibodies have been introduced: antibody avidity to a specific antigen is lower in patients with recent infection and higher avidity in older infection. The dissociation test can distinguish low-avidity test antibodies (seen in recently acquired infection) from high-avidity antibodies (seen in infections >4 months old). Although there is a consensus that a high-avidity index can rule out acute infection, the interpretation of a low-avidity index is less clear [8].

IgM antibodies: may appear earlier and decline more rapidly than IgG antibodies. False positives may result in cross-reactivity with rheumatoid factor (RF) and antinuclear antibodies (ANA). A major problem with a positive IgM test is the lack of specificity. A positive IgM is not an accurate marker of acute infection; it may persist for at least 12 years after acute infection. Also, another complication is the fact that several methods have a high frequency of false-positive results. Due to difficulties establishing an acute diagnosis in the immunocompromised, pregnant, or neonatal individual, it is suggested to follow up with infectious diseases or maternal-fetal specialist. An algorithm from the Centers for Disease Control and Prevention (CDC) for the immunodiagnosis of toxoplasmosis is shown below (Table 1).

IgA antibodies: may be detected in serum of congenitally infected neonates or in an acutely infected adults. This antibody can also remain positive for several months or even a year. This test is more useful in diagnosing congenitally acquired toxoplasmosis in the fetus and newborn.

IgE antibodies: can be used to diagnose toxoplasmosis in acutely infected newborn (congenital toxoplasmosis), children with congenital toxoplasma chorioretinitis, or adults. The duration of persistence of this antibody is less than IgM or IgA and may be useful in identifying recently acquired infection.

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Table 1 Interpretation of immunodiagnosis of toxoplasmosis

IgG result	IgM result	Report/interpretation for humans
Negative	Negative	No serological evidence of infection with *Toxoplasma*
Negative	Equivocal	Possible early acute infection or false-positive IgM reaction. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same, the patient is probably not infected with *Toxoplasma*
Negative	Positive	Possible acute infection or false-positive IgM result. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same, the IgM reaction is probably a false-positive
Equivocal	Negative	Indeterminate: Obtain a new specimen for testing or retest this specimen for IgG in a different assay
Equivocal	Equivocal	Indeterminate: Obtain a new specimen for both IgG and IgM testing
Equivocal	Positive	Possible acute infection with *Toxoplasma*. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same or if the IgG becomes positive, both specimens should be sent to a reference laboratory with experience in diagnosis of toxoplasmosis for further testing
Positive	Negative	Infected with *Toxoplasma* for more than 1 year
Positive	Equivocal	Infected with *Toxoplasma* for probably more than 1 year or false-positive IgM reaction. Obtain a new specimen for IgM testing. If results with the second specimen remain the same, both specimens should be sent to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing
Positive	Positive	Possible recent infection within the last 12 months or false-positive IgM reaction. Send the specimen to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing

http://www.cdc.gov/parasites/toxoplasmosis/

Polymerase chain reaction (PCR): has been used to detect *T. gondii* in various biological specimens such as CSF, vitreous/aqueous fluids, bronchoalveolar lavage (BAL) fluids, blood, and other tissues. PCR in blood samples appears to be a sensitive method for diagnosis of disseminated and cerebral toxoplasmosis [9].

When an individual gets exposed to *T. gondii*, any antibody test will be able to determine the presence or absence of the infection. A more difficult task is to determine whether an individual has acquired the infection recently or in the past. A true-negative IgM test effectively rules out a recent infection, but a positive IgM serology test might not be a representative of a recent infection; therefore, confirmatory tests should be performed.

Acute infection is suggested when there is a greater than fourfold rise in the IgG antibody in serum run in parallel or when there is a seroconversion of IgG and IgM antibodies from negative to positive. A single titer either IgG or IgM is insufficient to make a diagnosis of acute toxoplasmosis, so a confirmatory test is strongly suggested to rule out acute infection.

IgA antibodies are superior and more sensitive than IgM in the peripheral blood of newborn babies. It is strongly suggested to repeat another IgA at least 2 weeks apart to verify that no maternal contamination has occurred. Maternally acquired IgG antibodies should disappear between 6 and 12 months of life.

Treatment

In immunocompetent hosts: treatment is not necessary unless symptoms are severe or they persist for several weeks. Usually a lower dosage is used than with immunocompromised hosts. Therapy is used for about 2–4 weeks. Treatment consists of pyrimethamine (100 mg loading dose, then 25–50 mg daily) in association with sulfadiazine (2–4 g/day orally three times a day). All patients receiving pyrimethamine need to receive leucovorin calcium (folinic acid 10–25 mg/day). Other alternatives are pyrimethamine with clindamycin (300 mg orally four times a day), pyrimethamine with azithromycin (500 mg orally

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daily), pyrimethamine with atovaquone (750 mg twice a day), and trimethoprim (10 mg/kg/day) with sulfamethoxazole (50 mg/kg day) T-S twice daily.

In immunosuppressed hosts: Higher doses are required for 6 weeks. After this therapy, dosage is reduced for chronic management (this regimen is for patients who respond well to therapy). For patients who deteriorate clinically in the first 48 h of initial therapy, or develop elevated intracranial pressure, or CNS midline shift, dexamethasone (4 mg every 6 h) should be used. Monitoring patients at this time should not be based on IgG serology but with clinical, neurological, and radiological modalities. If the patient does not improve in 10–14 days after therapy is started, then consideration for an alternative diagnosis needs to be made. Treatment consists of pyrimethamine (200 mg loading dose, then 50–75 mg daily), as well as leucovorin (10–25 mg daily), in association with sulfadiazine (1 g orally four time daily); initially therapy is for 6 weeks. Alternative therapy might include T-S (5 mg/kg of trimethoprim or 25 mg/kg of sulfamethoxazole) twice daily, pyrimethamine with azithromycin (1 g orally daily), pyrimethamine with atovaquone (1.5 g twice daily), and sulfamethoxazole with atovaquone. For severe inflammatory processes, dexamethasone may be considered in a dose of 4 mg orally every 6 h. The use of medication for primary prophylaxis is when the CD4 falls below 100 cell/ml.

In ocular toxoplasmosis, most ophthalmologists elect not to treat due to the fact that these lesions are old inactive ones or scars. If decision to treat is done by an experienced ophthalmologist, then pyrimethamine with sulfadiazine in association to leucovorin for 4–6 weeks is adequate. Consideration for use of a steroid is made on a case-by-case basis.

During pregnancy: If toxoplasma is identified by serology due to maternal symptomatology, then treatment is justified. Prenatal treatment reduces serious neurological sequelae of congenital toxoplasmosis but does not affect ocular disease, vision, or mother-to-child transmission. Conventional therapy is with spiramycin (1 g orally every 8 h) alone; another alternative is pyrimethamine with sulfadiazine (P-S) in association with leucovorin. P-S is no more effective than spiramycin. There is no evidence that early treatment reduces risk of intracranial lesions or chorioretinitis. Also, there is no evidence that prenatal treatment reduces the risk of chorioretinitis. There is clear evidence that there is a reduction in serious neurological sequelae [9]. Alternative regimens include using pyrimethamine (50 mg daily) with sulfadiazine (3 g /day twice daily) for 3 weeks and then alternating with spiramycin (1 g orally daily) for another 3 weeks until baby is delivered. Leucovorin is added when P-S regimen is used.

Neonates: Infants with congenital infection should be treated with P-S and leucovorin for 21 days and then followed by either azithromycin or spiramycin for 4–6 weeks. Alternating P-S with macrolides should be continued for a minimum of 6 months, although generally is continued for 1 year. If neonate has elevated protein in the CSF or has chorioretinitis, then prednisone (1 mg/kg/day) may be added. Healthy newborns delivered to mothers with elevated antibody titers should be treated with a macrolide alone, until serologic evidence for the diagnosis of T. Gondii is definite [10].

Trichinellosis

Trichinellosis cases are much less common now than in the past. However, every year, approximately 20 cases are reported to Centers for Disease Control and Prevention (CDC) [11].

Etiology and Epidemiology

Trichinella spiralis, an intestinal nematode, is a common cause of trichinellosis. At present, 12 taxa including eight species and four genotypes (T6, 8, 9, 12) are recognized in the genus *Trichinella*. These taxa are divided into those that encapsulate in host muscle tissue and those do not encapsulate (T. *pseudospiralis*, *T. papuae*, and *T. zimbabwensis*). Among these, only six species and one genotype have been detected in humans.

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T. spiralis has a worldwide distribution, and pigs, rodents, and carnivores (e.g., fox, wild boar) are common hosts. *T. nativa* is common in arctic bears and walruses. *T. murelli* is common in carnivores in the USA and South Canada. *T. britovi* is common in carnivores and swine in Europe, Asia, and Africa. *T. papuae* is common in crocodiles and pig in Australia and Southeast Asia. *T. pseudospiralis* is common in swine, carnivorous birds, and animals in Europe [12].

In the USA, most swine are fed grain. Only a small proportion of swine are fed garbage. Those that are fed garbage may become infected with *T. spiralis*. Viable larvae in inadequately cooked meats particularly pork and wild game meats are ingested, passed into small intestine, and attached to the intestinal mucosal villi; once there, they develop into adult worms that mate and produce more larvae, which seed the skeletal muscles via the blood and lymphatic stream.

Clinical Features

Infection can be divided into an intestinal (enteral) and muscular (parenteral) phase. Clinical infection may range from asymptomatic/subclinical to severe disease based on the larvae ingestion. Most infections are subclinical (< 70 larvae). After ingestion, larvae migrate from intestinal mucosa to blood vessels, where they spread through the body, reaching striated skeletal muscle [13]. Infection with a heavy load (75–150 larvae) may lead to clinical features of the enteric phase including diarrhea (most common), abdominal discomfort, and vomiting. The parenteral phase usually begins 1–6 weeks after ingestion of the larvae and may present with fever (54%), myalgia (70%), facial or periorbital edema (28%), headache, fatigue, and weakness [14]. Conjunctivitis, subungual hemorrhages (vasculitis), and maculopapular rash may be also observed [15]. The differential diagnosis of trichinellosis includes influenza, dermatomyositis, and viral gastroenteritis.

A history of recent consumption of raw or undercooked meat should raise suspicion for the diagnosis of trichinosis.

Laboratory Diagnosis

Eosinophilia is often seen about the second week of illness and may reach very high levels. Serum creatinine phosphokinase and lactate dehydrogenase levels may be elevated when muscles are involved.

Organism-specific antibodies are generally detectable by 3 weeks after infection. Specific antibodies are usually measured by ELISA or immunofluorescence, further confirmed with the Western blot. If the diagnosis is still in doubt, muscle biopsy may be obtained from a tender, swollen muscle to detect larvae.

Treatment

The mainstay treatment for trichinosis is anthelmintic, salicylates, and bed rest. The main anthelmintic drugs used against trichinellosis are albendazole (15 mg/kg/day in two doses for 10–15 days) or mebendazole (200–400 mg orally three times a day for 3 days, then 400–500 mg three times a day for 10 days – not available in the USA). These drugs are contraindicated in pregnancy and in children less than 2 years of age. Treatment is effective if given in early stages of infection. Jarisch-Herxheimer-like reactions have been reported with these drugs in severe infestations due to massive release of antigenic substances. Prednisone (30–60 mg/day for 10–15 days) may be used in severely ill patients. Heating meat in a microwave oven, curing, drying, and smoking meat are not effective methods to inactivate Trichinella larvae [13].

Prevention

The mainstay of prevention of trichinosis is the proper cooking of meats. Although *Trichinella* larvae can be killed at 55 °C, meats should be cooked to reach a core temperature of 71 °C for at least 1 min until there is no trace of pink fluid or flesh. Exposure to freezing temperatures of −15 °C or lower for 3 weeks also sterilizes pork infected with *T. spiralis*.

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Lyme Disease

Etiology and Epidemiology

Lyme disease (LD) is the most commonly reported tick-borne disease in the United States and Europe. It was initially diagnosed in the town of Lyme, Connecticut in 1977, after an unusual cluster of what appeared to be juvenile rheumatoid arthritis. LD is caused by the spirochete *Borrelia burgdorferi* (Bb) and rarely, *Borrelia mayonii* in the United States; *Borrelia afzelii* and *Borrelia garinii* are the most common in Europe and Asia. Borrelia is a Gram negative spirochete bacterium. Bb is transmitted by the deer tick *Ixodes scapularis* (blacklegged tick) in the East, mid-Atlantic, and Upper Midwest and by the *Ixodes pacificus* in the West Coast of the USA. *Ixodes ricinus* is the major European vector. These vector ticks are forest dwellers, spending most of their time hiding in the leaf litter of the forest floor, where humidity is high and the risk of desiccation is low. Thus, Lyme disease is associated with heavily forested areas of the northern hemisphere.

Most cases of LD in the USA occur in southern New England, southeast New York, New Jersey, eastern Pennsylvania, eastern Maryland, Delaware, and parts of Minnesota and Michigan. The *I. scapularis* tick has a 2-year, three-stage life cycle: The larvae emerge from eggs laid in spring, hatch in early autumn, take their first meal, and become infected with spirochetes. Larvae molt into nymphs and during the next spring and summer takes their second meal (most likely to transmit infection). In late summer, they transform into adult forms, and they take their third meal (also infectious). They then reproduce, thus repeating the life cycle again. Approximately 30% of nymphal and up to 50% of adult female I. scapularis are infected in some areas [16]. Most humans are infected through the bites of nymphs and they are tiny (less than 2 mm) and difficult to see. Adult ticks can also transmit Lyme disease bacteria, but they are much larger and are more likely to be discovered and removed before they have had time to transmit the bacteria (Fig. 1).

Several factors are associated with the risk of transmission of Bb from ticks to humans. The tick must be infected; a critical factor is the duration of tick attachment, the tick feeds, and becomes engorged, discharging its saliva into the bite wound. The bacteria live in the midgut of the tick, which needs to be engorged with blood before migrate to the salivary gland and the saliva, then the organism is injected into the host [17]. The proportion of infected ticks varies greatly both in geographic area and the stage of the tick in its life cycle. How long the tick is attached (36–48 h) and whether or not it is engorged are two of the most important factors to consider when assessing the risk of transmission to humans.

Clinical Presentation

Lyme disease is classified into three different stages: early localized disease, early disseminated disease, and late disseminated disease. It is diagnosed in patients who have been previously exposed to an infected tick and who subsequently develop the typical signs and symptoms associated with LD affecting the skin, central nervous system (CNS), musculoskeletal system, and cardiac system.

Early localized disease will manifest as erythema migrans (EM), which appears at the site of the tick bite, usually within 7 to 14 days after the bite (range 3–30 days). It is classically reported as a single lesion, uniform erythematous, and oval to circular rash with a median of 16 cm (5–70 cm), and it expands for several days to weeks to form a large annular erythematous lesion. The lesion is usually asymptomatic but may be pruritic and has associated symptoms such as fever, malaise, headaches, lymphadenopathy, and myalgia. The EM lesion is pathognomonic of Lyme disease and it occurs in approximately 80% of patients. It is important to note that a skin lesion indistinguishable from EM occurs in Southern tick-associated rash illness (STARI), and it is found in the southeast and south central regions of the United States.

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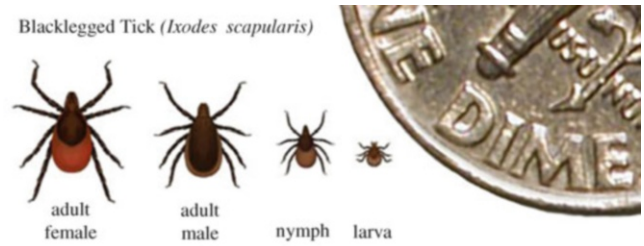


Fig. 1 Relative sizes of blacklegged ticks at different life stages. (Adopted from CDC)

Early disseminated disease usually occurs weeks to several months after the tick bite and may be the first manifestation of Lyme disease. The patient presents with multiple EM lesions; these lesions are smaller but morphologically similar to the initial lesion (EM). Another skin manifestation, called Borrelia lymphocytoma, a bluish-red nodule appearing usually on the earlobe or nipples within months or years of an infection can be seen in LD reported from Europe [18]. After the initial stage, the spirochete disseminates systemically via lymphatic system or bloodstream, it affects extracutaneous sites such as joints, CNS, and cardiovascular system. Common manifestations of early disseminated disease are migratory arthralgia (arthritis is usually a manifestation of late disease), which is reported in 60% of untreated patients. Neurologic involvement may include lymphocytic meningitis and cranial neuropathy – usually unilateral facial nerve palsy. Motor or painful sensory radiculoneuropathy known as Bannwarth's syndrome is more common in Europe. Lyme disease should be in the differential diagnosis in the etiology of Bell's palsy in endemic areas. Cardiac involvement, such as atrioventricular nodal block or myopericarditis, is less common.

Late disseminated disease occurs months to years after the tick bite. The patient presents either as chronic arthritis (monoarticular or oligoarticular) or neurological symptoms (encephalomyelitis or peripheral neuropathy). Approximately 60% of untreated patients develop intermittent arthritis and 10% develop persistent monoarthritis usually affecting the knee [19]. Other late manifestation including Acrodermatitis chronica atrophicans, a chronic sclerosing dermatitis, develops in patients infected with *B. afzelii* an uncommon manifestation in Europe. It is usually located in the lower extremities and progresses slowly. The initial inflammatory phase is characteristic with a bluish-red discoloration of the skin located in the distal parts of extremities, which then progresses to the atrophic phase, with epidermal thinning.

Post-Lyme symptomatology is characterized by symptoms and complaints for more than 6 months after adequate treatment. Musculoskeletal or radicular pain, dysesthesias, neurocognitive symptoms, sleep abnormalities, and fatigue have all been reported. No additional antimicrobial therapy is effective at this stage, but symptomatic management is recommended.

Serologic testing is an important tool for the diagnosis of Lyme disease. The Centers for Disease Control and Prevention (CDC) recommends serologic evaluation as the preferred initial diagnostic test. Serologic testing should be performed in patients who meet **all** of the following criteria: A recent history of having resided in or traveled to an area endemic for Lyme disease, risk factor for exposure to ticks, and having **s**ymptoms consistent with early disseminated disease or late Lyme disease (e.g., meningitis, radiculopathy, mononeuritis, cranial nerve palsy, arthritis, and carditis). Serologic testing should **not** be performed for screening of asymptomatic patients living in endemic areas or patients with nonspecific symptoms only, due to greater chance of false-positive test results than true positive test results.

A two-tiered protocol using an enzyme-linked immunosorbent assay (ELISA) is initially followed by a more specific Western blot to confirm the diagnosis when the assay is positive or equivocal. If the ELISA test is negative, an immunoblot is not necessary. The ELISA test provides quantitative estimate of antibodies against

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Bb. The immunoblot produces information about specific proteins against Bb that are present (band). In order for a Western blot to be considered positive, it requires to have either two bands for IgM or five bands for IgG. Urine antigen testing is not recommended [20]. IgM antibodies usually appear 2–4 weeks after infection, peak at 8–10 weeks after infection, and gradually disappear, but in some patients, these may persist for several years. IgG antibodies appear after 6 weeks postinfection, peak after 4–6 months, and still are detectable after several years. A diagnosis of Lyme disease should not be based solely on a positive serology (IgM), but on epidemiological data, as well as physical examination, since IgM and IgG may persist for years after effective treatment of LD.

Polymerase chain reaction (PCR) test can be done in synovial fluid and cerebrospinal fluid in patients with untreated Lyme arthritis and meningoencephalitis [21]. FDA does not approve urine and blood specimens for PCR testing due to limitations [22]. False-negative PCR results can occur due to the presence of inhibitors of the DNA polymerase, such as hemoglobin or hyaluronic acid. The accuracy of PCR is highly dependent upon the care used in sample collection and storage and the technique used in the assay.

Culture remains the diagnostic standard. Although it is not routinely available, it is useful in biopsy samples of EM lesions or plasma in multiple EM lesions. This is due to the fact that EM appears 3–30 days after the tick bite, while Bb antibodies appear 2–4 weeks after the bite. Individuals with EM may have negative serology but positive spirochetes in the blood.

Treatment

Early localized disease characterized by EM is best treated with an oral antibiotic. Adults should receive doxycycline (100 mg twice a day), or amoxicillin (500 mg three times a day), or cefuroxime (500 mg twice a day), or azithromycin (500 mg daily). Children older than 8 years of age can receive doxycycline (4 mg/kg/day twice a day, maximum dose 100 mg twice a day), and younger children should receive amoxicillin (50 mg/kg/day in three doses, maximum 500 mg per dose) or cefuroxime (30 mg/kg/day in two doses, maximum 500 mg per dose) or azithromycin (10 mg/kg/day, maximum 500 mg per dose). Doxycycline is contraindicated in pregnancy and breastfeeding and in children younger than 8 years old. All of the above treatments should be for 14 days.

Early Disseminated Disease: Multiple EM, localized cranial nerve palsy, or carditis without heart block can also be treated with oral antibiotics. Parenteral ceftriaxone (2 g IV daily) in adults or children (50 mg/kg/day) is used for treatment of Lyme meningitis, myocarditis, and heart block in symptomatic individuals requiring hospitalization. Once symptomatology improves, then oral therapy is completed. Therapy is for 14–28 days.

Late disease such as arthritis, without neurologic involvement, can be treated with oral antibiotics as used for EM, but treatment should be prolonged for up to 28 days. Patients with neurologic symptoms including encephalitis, encephalomyelitis, or peripheral neuropathy with or without arthritis should be treated with parenteral antibiotics as in early-disseminated disease for 14–28 days.

A Jarisch-Herxheimer reaction may develop after therapy is initiated (fever, sweating, myositis). In this case, the medications are generally continued, and nonsteroidal anti-inflammatory drugs are often beneficial.

Post-Lyme disease symptoms are difficult to treat. Randomized controlled trials of repeat antimicrobial therapy in such patients have **not** shown a sustained benefit of prolonged antimicrobial therapy. The most common reason for lack of response to appropriate antimicrobial therapy used to treat LD is misdiagnosis (the patient does not have Lyme infection). The knee synovitis of Lyme disease may persist for months after antibiotic therapy possibly due to the triggering of an autoimmune process [23, 24]. Nonspecific symptoms (fatigue, arthralgia, or neurological maladies) may persist for several weeks even with successful treatment and should be treated with nonsteroidal anti-inflammatory medications.

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Ebola and Marburg Virus

Etiology and Epidemiology

Ebola (EBV) and Marburg viruses (MARV) are the members of family *Filoviridae*, causing Ebola virus disease and Marburg disease in humans and primates. The genus Ebolavirus consists of five species: Zaire, Sudan, Bundibugyo, Tai Forest, and Reston. They are named according to the location of the first outbreak recorded by this strain. The outbreak caused by the Zaire species in Central Arica has the highest case fatality rate (80–90%). The same virus was the causative agent of the 2014–2016 epidemic in West Africa; in which, there were nearly 29,000 total cases (suspected, probable or confirmed) and case fatality rate was approximately 40%. Since then, the Zaire species has been responsible for three epidemics in the Democratic Republic of the Congo in 2017 and 2018. MARV consists of a single species: Lake Victoria MARV (Fig. 2).

Ebola and Marburg viruses are single-stranded RNA viruses. In the past, those were classified as "hemorrhagic fever viruses" based on their clinical manifestations which include bleeding and shock. But only a small percentage of patients developed significant bleeding, which usually occur in terminal phase of illness. Therefore, the term "hemorrhagic fever" is no longer used. The filoviruses were first recognized in 1967, when the inadvertent importation of infected monkeys from Uganda resulted in outbreak of illness among vaccine plant workers in Marburg, Germany. MARV is often introduced into human by people who enter cave and mines. EBV may be introduced by hunting or processing meat. Bats can act as host and are reservoir for filoviruses. The transmission pathway from bats to humans and the possible role of bats in the initiation of Ebola outbreaks have not been identified so far.

The virus spreads through direct contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth) with blood or body fluids (urine, saliva, sweat, feces, vomit, breast milk, and semen) of a person who is sick with or has died from Ebola Virus Disease, and can remain in certain bodily fluids-including semen, even if the patient no longer have symptoms of severe illness. Ebola virus can be transmitted via contaminated objects (such as needles and syringes), infected fruit bats, or nonhuman primates (such as apes and monkeys).

Ebola virus infects many different cell types including endothelial cells, fibroblasts, hepatocytes adrenal cortical cells, and epithelial cell, causing necrosis. It attacks macrophages and dendritic cells first, and then it is carried to regional lymph nodes via lymphatics and subsequently to the liver, spleen, thymus, and other lymphoid tissues via the blood stream. Fatal disease is characterized by multifocal necrosis in tissues such as liver and spleen.

Immediately upon a person's entrance to the ED, or in advance of entry if possible, a thorough history of international travel or contact with an individual with EVD within the previous 21 days should be obtained. Patients who meet the exposure criteria should be questioned regarding the presence of signs or symptoms compatible with EVD including: fever (subjective or $\geq$ 100.4 °F or 38.0 °C), headache, fatigue, weakness, muscle pain, vomiting, diarrhea, abdominal pain, or hemorrhage (bleeding gums, blood in urine, nose bleeds, coffee ground emesis or melena). If the patient meets both exposure risk factor and clinical criteria, isolate the patient in a private room or in a separate enclosed area with private bathroom with covered bedside commode and adhere to procedures and precautions designed to prevent transmission either by direct or indirect contact. Detailed recommendation and guideline can be found at https://www.cdc.gov/vhf/ebola. If Ebola virus disease is suspected, local or state health department should be immediately contacted for consultation and to assess whether or not testing is indicated and the need for initiating identification of contacts [25].

Clinical Presentation

Patients with Ebola virus disease typically have an abrupt onset of symptoms 6–12 days after exposure (range 2–21 days). There is no evidence that infected persons who are asymptomatic are

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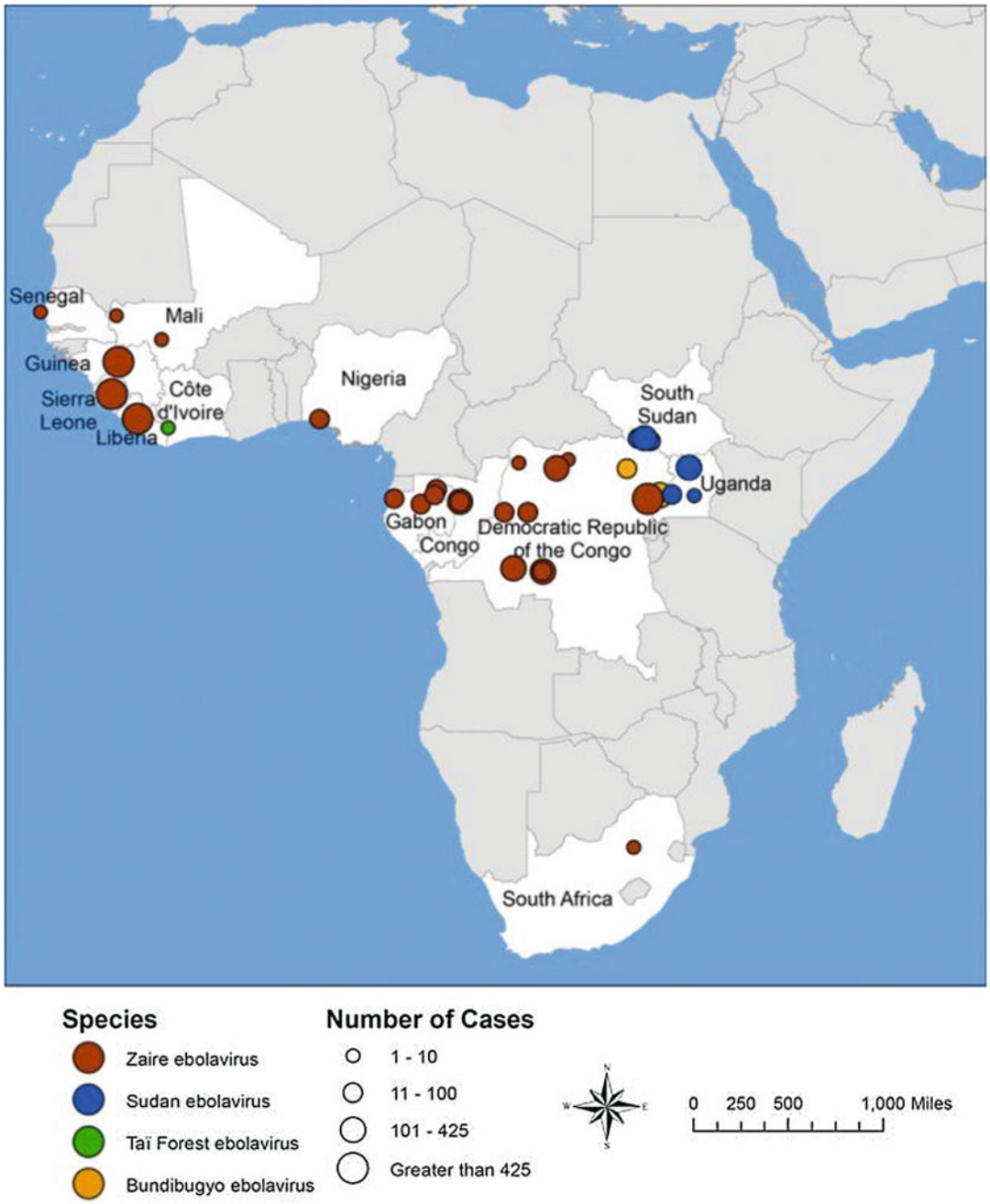


Fig. 2 Ebola virus outbreaks by species and size, Since 1976. (From CDC- Center for Disease Control and Prevention website)

infectious to others. However, all symptomatic individuals should be assumed to have virus in the blood or other body fluids, and appropriate safety precautions should be taken. Common signs and symptoms include fever (87%), fatigue (76%), vomiting (67%), and diarrhea (66%), loss of appetite (65%), abdominal pain (45%), and unexplained bleeding (18%) and also may

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present with cough, rhinorrhea, headache, or myalgia [26].

In the 2014 outbreak, the primary clinical presentation was gastrointestinal symptoms developing within the first few days of illness. Vomiting and diarrhea may result in severe fluid loss, leading to dehydration, hypotension, and shock. A diffuse erythematous, nonpruritic maculopapular rash may develop by day 5 to 7 of illness. The rash usually involves the face, neck, trunk, and arms. Hemorrhagic manifestations include blood in the stool, petechiae, ecchymosis, oozing from venipuncture sites and /or mucosal bleeding. Clinically significant hemorrhage may be seen in the terminal phase of illness and in pregnancy. Patients occasionally develop meningoencephalitis, with findings of altered mental status, hyperreflexia, neck stiffness, and gait instability. Other manifestations include uveitis, relative bradycardia, myocarditis, pericarditis, hypoxia, hypoventilation due to respiratory muscle fatigue contributing to respiratory failure.

Altered mental status, shock, and bleeding are poor prognostic factors. Major causes of death are due to electrolyte imbalance, shock, and multiorgan failure. Contacts are observed for 21 days and need not to be isolated before onset of symptoms. In the initial stages of presentation, Ebola virus disease is easily confused with influenza, gastroenteritis, malaria, typhoid, and other bacterial infections.

Laboratory Diagnosis

Patients with Ebola virus disease typically develop leukopenia, thrombocytopenia, transaminases elevation, renal and coagulation abnormalities [27]. Diagnosis can be made by detection of viral genome by reverse transcription polymerase chain reaction (RT-PCR). The Ebola virus is generally detectable in blood specimen by RT-PCR within 3 days after onset of symptoms. A repeat testing may be needed for patients with symptoms for fewer than 3 days [28]. According to CDC guidelines, a negative RT-PCR test that is collected >72 h after the onset of symptoms excludes Ebola virus disease [29].

Antigen capture ELISA may be also used. A rapid lateral-flow chromatographic immunoassay (ReEBOV) can detect Ebola virus antigen within 15 min, with sensitivity of 80–98% and specificity of 80–100%. A second Ebola rapid antigen finger stick test was approved by FDA in November 2018. This test uses a portable battery-operated reader that allowed to be performed at point of care outside of the laboratory.

Immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies are detected by ELISA later in the disease course or after recovery.

Treatment

The mainstay of treatment for Ebola virus disease involves supportive care in order to maintain adequate organ function (e.g., cardiovascular, respiratory, or renal) while the immune system mobilizes an adaptive response to eliminate the infection [27]. They should receive care in designated treatment centers and by clinician trained to care for such patients.

Patients may lose large amounts of fluid through vomiting and diarrhea, requiring rapid volume replacement to prevent shock; antiemetic and antidiarrheal agents may also be beneficial. Careful attention balancing intake with fluid losses will assist with fluid repletion targets. When available, patients will benefit from hemodynamic monitoring and intravenous (IV) fluid repletion. However, patients in the early phase of illness who respond to oral antiemetic and antidiarrheal therapy may be able to take in sufficient fluids by mouth to prevent or correct dehydration. Patients may develop significant electrolyte disturbances (e.g., hyponatremia, hypokalemia, hypomagnesemia, and hypocalcemia) and may require frequent repletion of electrolytes to prevent cardiac arrhythmias.

There are no approved medications for treatment of Ebola virus disease or for use as post exposure prophylaxis in persons who have been exposed to the virus but have not yet become ill. The 2014–2016 West African outbreaks focused attention on the potential anti-Ebola activity of drugs that were developed for other purposes. In

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addition, it accelerated the evaluation of experimental therapies that had been developed to treat or prevent Ebola or Marburg virus infection and had demonstrated efficacy in laboratory animals.

Investigational drugs include monoclonal antibodies (mAb114, REGN-EB3, and ZMapp) and nucleotide analogues (GS-5734, also known as remdesivir). The novel nucleotide analogue prodrug remdesivir was highly efficacious in macaques infected with Ebola virus, even when initiated 3 days after virus challenge. Studies of tissue distribution indicated drug penetration to the testes and central nervous system. Remdesivir, together with ZMapp, was also used to treat a newborn baby infected with Ebola virus in Guinea, near the end of the West African epidemic [30].

Prevention

Practice careful hygiene when in an epidemic area. Patient isolation and full-body protective clothing are required to prevent contact with infected body fluids. Healthcare personnel should wear appropriate personal protective equipment (PPE): disposable water-resistant coveralls, a waterproof apron or impermeable gown, an N95 mask, a disposable full face shield, two sets of gloves, and impermeable foot and leg coverings. It is recommended to use a powered air purifier respirator suit (PAPR) when performing medical procedures like intubation or airway suctioning. Avoid handling the body in burial or funeral rituals of people who have died from Ebola.

No approved vaccines are available to prevent the spread of Ebola virus. However, during the 2014–2016 epidemic in West Africa, accelerated paths were developed for vaccine testing and introduction into field use. The recombinant vesicular stomatitis virus-Zaire Ebola (VSV-Ebola) virus vaccine has been most widely used. The VSV-Ebola vaccine was the only specific countermeasure reported to have protective efficacy against Ebola virus during the 2014–2016 West African epidemic. In a large trial of ring vaccination in Guinea, the VSV-Ebola vaccine was safe and effective in inducing rapid immunity against Ebola virus [31].

In the Democratic Republic of the Congo (DRC), the VSV-Ebola vaccine was administered to nearly 4000 people during the outbreak in the Equateur Province of the DRC that occurred from May to July 2018. It has been used even more extensively in the ongoing epidemic in the eastern DRC, with more than 130,000 people vaccinated as of June 8, 2019. The vaccine is also being given to health care workers in South Sudan and Uganda, bordering on the outbreak area in the DRC. A survey of recipients in the outbreak area in the eastern DRC found that the vaccine was well tolerated and accepted by the local community.

Hantaviruses

Etiology and Epidemiology

Hantavirus is one of the major classes of zoonotic pathogens and is a member of the *Bunyaviridae* family, which are single-stranded RNA viruses. The resulting diseases can cause significant morbidity and mortality and occur globally. Rodents of the families Muridae and Cricetidae carry medically important Hantaviruses. These pathogens are associated with two severe acute febrile illnesses: Hemorrhagic fever with renal syndrome (HFRS) and Hantavirus cardiopulmonary syndrome (HCPS), the latter is also known as Hantavirus pulmonary syndrome (HPS). The important Hanta viruses which are associated with human disease include Hantaan, Seoul, Dobrava, Puumala, Sin Nombre, Black Creek Canal, New York, Bayou, Andes, Laguna Negra, Choclo, and Rio Mamore. The first four are associated with HFRS and the rest are associated with HCPS.

Hantavirus is named after the Korean River, Hantaan, where the first outbreak was reported in 1951(Korean hemorrhagic fever). China bears the highest annual incidence by far of Hantavirus disease. More than 100,000 cases of HFRS are reported every year in China, and thousands of cases are likely to occur in Russia. Chinese cases of HFRS are most commonly caused by Seoul

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virus, with some cases caused by Hantaan virus. Several thousand cases of HFRS due to Puumala and Dobrava viruses occur annually throughout Europe.

In the United States, HCPS is the major clinical presentation of Hanta virus disease. As of January 2017, 728 cases of Hanta virus disease had been reported within the United States, with more cases in the western and southwestern states such as New Mexico, Arizona, California, Washington, Colorado, Montana, and Texas. There have been outbreaks in the Southwest in 1993 (Sin Nombre) and in Yosemite National Park, California, in 2012. HFRS due to Seoul virus is rarely observed in the United States, but an outbreak of Seoul virus occurred in rat breeders and pet rat in Wisconsin in 2017.

Canada reports 10 to 15% of North American cases each year. Other countries that have experienced hantavirus activity include Argentina, Bolivia, Brazil, Chile, Ecuador, French Guiana, Panama, Paraguay, Peru, Uruguay, and Venezuela. Collectively, more than 3000 cases of HCPS have been identified throughout the Americas, far less than the Eurasian total for HFRS. The case-fatality ratios are much higher for HCPS (25 to 50%) than for HFRS (about 15%).

Rodent contact is an important factor in the transmission of hantaviruses to humans. Many hantaviruses are shed in the urine, feces, or saliva of acutely infected reservoir rodents. It is suspected that transmission to humans occurs via the aerosol route. Very few patients who contract hantaviruses describe recent rodent bites. Indoor exposure may be especially important. Human-to-human transmission of hantavirus is exceedingly rare but possible. Recent findings indicate that bats, moles, shrews, and other mammals may also serve as hosts.

Clinical Presentation

Typically, a period of 2 to 3 weeks elapses between exposure to a Hantavirus and the onset of symptoms. The incubation period is 14 to 17 days (range 9–33 days) [32]. Humans can be asymptomatic from the infection or develop severe reactions, in the form of either HFRS or HCPS. Early symptoms can be nonspecific with fever, fatigue, and generalized muscle aches, especially in the legs, back, and hips. Abdominal symptoms, headache, and dizziness may also occur during this early phase. These generalized symptoms resemble other viral syndromes and make early diagnosis difficult. Symptoms in the later phase of the infection with HCPS are cough and shortness of breath, which are due to pulmonary edema and hypotensive shock. Renal dysfunction/failure with hemorrhage occurs in HFRS [33]. These two syndromes may overlap. Age, gender, genetic response, and immune status can affect the prognosis. Males tend to get more symptoms than females, but females appear to have a higher mortality rate. Interestingly, infected rodents are not affected negatively by the virus.

Laboratory Findings

Associated laboratory findings are increased hematocrit, leukocytosis, thrombocytopenia, and elevated creatinine. Serology is the main stay of diagnostic method. By the time symptoms are evident, patients already have IgM antibodies and most of them have IgG antibodies [34]. IgM and IgG antibodies can be detected by using ELISA, strip immunoblot (SIA), or immunofluorescence techniques. The polymerase chain reaction (RT-PCR) can detect hantaviruses that cause fulminant infection with high case-fatality rates (Andes, Sin Nombre, Dobrava, and possibly Hantaan viruses) in blood specimen during the early stages of pulmonary disease. However, viral RNA usually disappears from the circulation after a few days, and serologic techniques have high diagnostic accuracy.

Treatment

Treatment is generally supportive, with earlier intervention leading to better outcomes. Survival increases with early recognition, hospitalization, and adequate pulmonary and hemodynamic support. This includes intensive care unit monitoring and the initiation of mechanical ventilation as

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needed to treat respiratory failure. Extracorporeal membrane oxygenation (ECMO) has been used with success. Given the role of capillary leak in the development of noncardiogenic pulmonary edema and hypotension, early use of vasopressors and inotropes for management of hypotension and cautious use of intravenous fluids is needed. Early dialysis helps in acute renal failure. Antiviral treatment is generally unsatisfactory for HCPS, whereas rivabirin may be effective against HFRS due to Hantaan virus. There is no role for glucocorticoid therapy in hantavirus diseases.

Prevention

In general, rodent control is the most important preventive measure, which can be done by sealing gaps/holes in homes, setting traps, and keeping food in enclosed containers. Seldom used buildings should be opened and aired out prior to entry. If heavy infestation is present in an area where HCPS has been reported, it is recommended that the appropriate local, state, or federal health officials be consulted prior to clean-up [35].

Unfortunately, only few vaccines are available worldwide. In China and Korea, killed-virus vaccines are available for Hantaan virus and/or Seoul virus [36]. No vaccines are available for Sin Nombre virus or other agents of HCPS.

Giardia

Giardia lamblia is a parasite capable of causing epidemic or sporadic diarrheal illness from contaminated water supplies, person to person (i.e., day care, mental institutions), contaminated food, or travelers where giardiasis is endemic. There is a high prevalence in developing countries with poor hygiene and poverty is high, and has a lower prevalence in industrialized nations.

Etiology and Epidemiology

Giardiasis is one of the most common intestinal protozoan infections in the world. The etiologic agent is *Giardia lamblia* (Giardia *duodenalis*, *Giardia intestinalis*), a flagellated protozoan which infects a wide array of hosts. It is the most common cause of waterborne outbreaks of diarrhea in the USA [37]. Ingestion of even 1–10 cysts can cause clinical disease. Infection occurs when cysts are ingested with contaminated water, food, or direct fecal-oral contact. Once in the stomach, the acid pH causes cysts to excyst into trophozoites in the proximal small intestine, where they replicate and cause diarrhea and malabsorption. The transmission cycle is complete when the trophozoites are exposed to biliary acid, transforming into cysts in the jejunum, and then are passed in the feces [38].

There are eight different genotypes within *G. lamblia*, but only two types are capable of infecting humans (A and B), dogs are infected with genotypes C and D, cats with F, and livestock with type E. Previous exposure to G genotype produces partial immunity to disease and leads to a reduced risk of reinfection and to reduced development of overt symptoms in secondary infection [39].

Clinical Presentation

The great majority of patients infected with *G. lamblia* are asymptomatic. Classical presentation usually begins 1–3 weeks after ingestion of cysts and includes abdominal pain and cramps, nausea, belching, bloating, flatulence with sulfur odor, and diarrhea. Fever and vomiting are rare, as are blood or mucus tinged feces. If patient remains untreated, diarrhea may persist for several months, having flare-ups of diarrheal disease interspersed with normal stools. Chronic infection can cause disaccharidase enzyme deficiency and brush-border damage causing fat malabsorption, lactose intolerance, vitamin A and K deficiency, and failure to thrive in children [40].

Laboratory Diagnosis

The microscopic ova and parasite (O&P) evaluation is the traditional method for stool parasite testing and is the cornerstone of diagnostic testing for intestinal protozoan evaluation. However,

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microscopy may be cumbersome and requires an experienced laboratory technologist. The Food and Drug Administration (FDA) has approved several detection tests for *Giardia*, *Cryptosporidium*, and *Entamoeba histolytica*. These advanced molecular assays offer fast and reliable results with appropriate sensitivity and specific for detections of multiple parasites [41].

Treatment

Several agents are used to treat giardia infection and include:

Nitroimidazoles: Tinidazole [Tindamax], adults 1 g daily for 1–2 days, children >3 years: 50 mg/kg/dose daily for 1 to 2 days; most side effects include nausea, abdominal pain, anorexia, and stomatitis. This medication is not indicated for children. Metronidazole (Flagyl) (adults 250 mg/dose two to three times a day for 5–10 days) is quickly and completely absorbed after oral administration. Despite its widespread and accepted use against *Giardia*, the Food and Drug Administration (FDA) has not approved it for this indication. This medication is well tolerated; the most common side effects are gastrointestinal upset and a metallic taste.

Furazolidone: Furazolidone (Furoxone) (adults 100 mg/dose four times a day, pediatrics 1.5 mg/kg/dose) is used for a 7- to 10-day course. It is approved for use against *Giardia*. Side effects might include nausea, vomiting, and diarrhea.

Benzimidazoles (Nitazoxanide): Albendazole (Albenza) (adults 400 mg/day for 5 days, pediatric dose 15 mg/kg/day) for 5–7 days. Mebendazole (Vermox) (adults and pediatrics 200–400 mg/day) for 5–10 days. One advantage of using albendazole is its efficacy against multiple helminths and relative lack of side effects.

Paromomycin: Paromomycin (Humatin) is indicated for treatment of *Entamoeba histolytica* and *Trichomonas*. It is used in treatment of *G. lamblia* in resistant infections and pregnancy [42].

Immunocompromised individuals, IgA deficiency, drug-resistant organisms may need larger doses and longer duration in order to eradicate this organism. Patients should be advised that a transient lactase deficiency is common with Giardiasis and to consider minimizing lactose-containing food for a few weeks.

Rocky Mountain Spotted Fever (RMSF)

Rocky Mountain Spotted Fever (RMSF) is a potentially fatal tick borne illness that occurs throughout the United States (US), Canada, Central America, and South America and is the most common rickettsial infection in the in the USA. With the ease of travel patients infected by RMSF may present to family physicians in nonendemic locations. Early diagnosis is critical since it has a high mortality rate if untreated.

Epidemiology

Rickettsia rickettsii, an obligatory intracellular gram negative rod-shaped bacterium, is the causative organism of RMSF; it is a zoonotic tick-borne disease (TBD) in which humans are accidental hosts. Ticks become infected by feeding on the blood of an infected animal, then pass it through their saliva to humans, as the organism invades the endothelial and smooth muscle cells of blood vessels thus causing vascular injury, and activation of inflammatory and coagulation cascades. Ticks serve as both the vector and the reservoir of *R. rickettsii* and vary based upon geographical location: *Dermacentor variabilis* (the American dog tick) is in the south central and eastern USA, *Dermacentor andersoni* (the Rocky Mountain wood tick) is in the mountain states west of the Mississippi River, *Rhipicephalu sanguineus* (the brown dog tick) is in Arizona and Mexico [43, 44], the Cayenne tick (*Amblyomma* cajennense) is in Central and South America, and the yellow dog tick (*Amblyomma aureolatum*) is in Brazil. There is a seasonal distribution (spring and summer); therefore, the majority of cases occurs during April through September, when humans increase their recreational outdoor activity [45].

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Clinical Features

Infected patients typically become symptomatic within 2 days to 2 weeks, and the initial diagnosis is based on clinical signs and symptoms. The early stages are characterized by fever (95–100%), headache (80–90%), gastrointestinal symptoms (60%) nausea, vomiting, anorexia, abdominal pain (can mimic appendicitis), myalgia, edema around the eyes and on the back of hands. Rash develops in the first 2–4 days of illness (56–88%); this blanching erythematous macular or papular rash usually starts on the ankles and wrists, then spreading to the soles and palms, and then centrally to the arms, legs, and trunk. Within 48–72 h it may become petechial (a sign of severe disease) or purpuric. The later stages of RMSF (day 5 or later) the rash can lead to necrosis and gangrene (thus requiring amputation). In some cases of RMSF (up to 10%), there is no rash present at all [44]. The late stages of the disease can result in multiorgan system damage: neurological damage (altered mental status, coma, meningismus, hearing loss, and encephalitis), respiratory compromise (acute respiratory distress, pulmonary edema, and pulmonary infiltrates), cardiac involvement (pericarditis, arrhythmias, and myocarditis), acute renal failure, coagulation defects, and gastrointestinal bleeding [45].

Laboratory Diagnosis

R. rickettsii cannot be cultured in most clinical laboratories, and therefore the diagnosis is mainly clinical. Most patients with RMSF have normal white blood cell count at presentation, and thrombocytopenia can occur as the disease progresses. In advanced cases, hyponatremia is frequently noted (common with CNS symptoms), elevations in serum aminotransferases, hyperbilirubinemia, azotemia, and prolongation of the partial thromboplastin and prothrombin times (PT and PTT) is also seen. The cerebrospinal fluid (CSF) may demonstrate pleocytosis and elevated CSF protein (33%) [44].

Indirect immunofluorescence (IFA) testing is the most widely available and frequently used test with an overall sensitivity of approximately 95% and seroconversion usually occurs 14 days after the onset of symptoms. The diagnostic titer is usually greater than 1:64, or a fourfold rise in the titers collected 2 weeks apart (between paired acute and convalescent sera). Confirmation of *R. rickettsii* antigen via skin biopsy with direct immunofluorescence, or identification of rickettsial DNA in blood or tissue sample by PCR is performed when available [44, 47].

Treatment

Treatment decision for rickettsial pathogens should never be delayed while awaiting for laboratory confirmation. Following tick removal, there are two antibiotics that have proven efficacy for treating RMSF: tetracycline (doxycycline) and chloramphenicol. Doxycycline is the drug of choice in all adults and pregnant women (100 mg twice daily for 7 days) and in children (2.2 mg/kg/dose twice daily for 5–14 days). Chloramphenicol is given when tetracycline are contraindicated (adult dosage is 50–100 mg/kg IV every 6 h and the pediatric dosage is 50–75 mg/kg/dose IV every 6 h). In cases with severe nausea and vomiting, IV hydration support is necessary. Antibiotics are generally stopped 48 h after the fever subsides [46], they are most effective when given within the first 5 days, but if left untreated for 8–15 days, death may occur in up to 20% of the patients. Risk factors for severe/fatal disease include children younger than 10 years old, adults older than 60 years of age, patients with G6PD deficiency, alcohol use, and male African-American patients [47].

Prevention

The most effective prevention is to avoid areas endemic for *R. rickettsii*. Other preventive measures include: Spraying yards with pesticides, assuring that all dogs have tick collars [63]), walking on the center of paths and trails, wearing clothing treated with 0.5% permethrin, treating the skin with tick repellants (DEET), daily full

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body checks, and using a dryer for at least 10 min for all of the clothing worn [45]. Careful removal of the ticks with forceps or covered hands, grasping the tick nearest to the head without compressing the body, and gently pulling straight outward can also help prevent RMSF [48, 49]. No data to date support the use of prophylactic antimicrobials in individuals after a recent tick bite without clinical illness.

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Epidemics and Pandemics

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Mark K. Huntington

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Introduction

Epidemics and pandemics are large-scale outbreaks of diseases that affect wide geographical areas; the former are more local, and the latter are international and potentially global. They cause significant morbidity and mortality and can have major impacts on society in a variety of ways. While noncommunicable diseases also cause pandemics (e.g., the obesity pandemic), traditionally the term is used to refer to infectious diseases, and that will be the focus of this chapter. Common usage of "outbreak" applies to the rapid emergence or spread of infectious disease; thus, the gradual emergence of disease, such as those caused by antibiotic-resistant organisms, is also outside the scope of this chapter. Table 1 lists some examples of pandemics of the past and present.

The emergence of an epidemic (and potentially, a subsequent pandemic) is the result of the convergence of four determinants: humans, pathogen, its natural host, and the environment (Fig. 1). The interplay between these determinants can alter the likelihood of the disease transmission to, and ultimately between, humans [1]. Increasing contact between the natural host and humans

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Table 1 Select notable pandemics [23–27]

Pandemic	Toll	Geography	Pathogen	Era
The Black Death	50% of Europe's population died	Europe primarily	*Yersinia pestis* (plague)	1346–1353
Smallpox	Up to 50% mortality	Americas primarily	Smallpox virus	1500s–1600s
"Russian" flu	1 million deaths	Global	Influenza virus	1889–1890
"Spanish" flu	500 million cases; 30–100 million deaths	Global	Influenza virus	1918–1920
"Asian" flu	1–2 million deaths	Global	Influenza virus	1957–1958
"Hong Kong" flu	500,000–1 million deaths	Global	Influenza virus	1968–1969
AIDS	35 million deaths (to date)	Global	Human immunodeficiency virus	1960–present
SARS	8098 cases; 774 deaths	Global	SARS virus	2003
2009 H1N1	1.4 billion cases; 500,000 deaths	Global	Influenza virus	2009–2010
Ebola	28,600 cases; 11,325 deaths	Africa primarily	Zaire ebolavirus	2014–2016
Dengue	100–400 million new cases annually	Global	Dengue virus	2000–present
Zika	Most significant morbidity results from prenatal exposure. Full impact unknown	Global	Zikavirus	2007–present
COVID-19	Full impact unknown	Global	SARS-CoV-2	2019–present

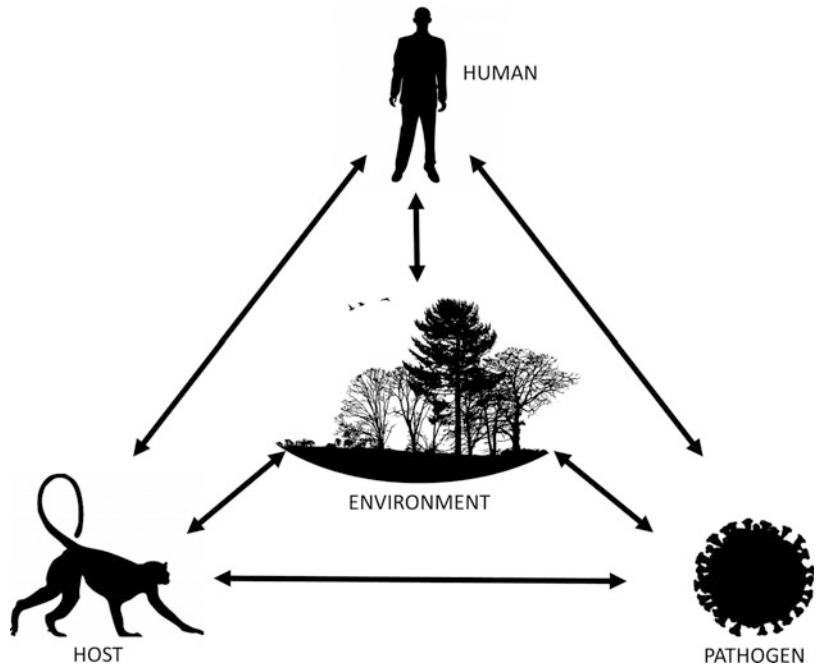


Fig. 1 The four determinants of a disease outbreak. Shifts in the interplay between these determinants may result in increased rates of infection and spread

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increases the likelihood of transmission – this is important, because nearly all pandemics in history can be classified as zoonoses. This contact can result from human encroachment into the hosts' habitat or habitat changes that increase the hosts' (or for some diseases, the vectors') population numbers. For most zoonotic pandemics, changes beyond mere contact are necessary. Alterations of the pathogens' receptor specificity, pH tolerance, enzyme activities, and ability to evade its new hosts' defensive mechanisms are also required [2]. Many pathogens sporadically cross over to infect humans; fortunately few succeed in clearing all of the hurdles necessary to establish themselves as communicable diseases capable of human pandemic potential.

Detection

Surveillance

Following the influenza pandemic of 1918, governments and private institutions around the world began active surveillance for influenza in an effort to detect – and attempt to prematurely terminate – the next pandemic. In the USA, these efforts are based in the Centers for Disease Control and Prevention (CDC). The surveillance strategy has several components, each implemented from a different perspective. These range from a purely clinical approach, to a microbiological research perspective, to a public health and geographic tracking strategy. These surveillance categories are summarized in Table 2.

A comprehensive surveillance system is of importance for a number of reasons. Disease strains can change rapidly; when an antigenically distinct organism enters an immunologically naïve population, it has the potential to cause a pandemic. This is especially true in the case of a dramatically different strain, as in the case of recent crossover to humans of a zoonotic influenza strain. Although to date no emergence of a novel pandemic strain has been announced by detection of a closely related precursor in an animal or human prior to the outbreak [3], changes in the dynamics of the epidemiology of human influenza could be the harbinger of such an event. National responses to emerging pandemic strains are triggered by surveillance data. These responses will be presented in greater detail later in this chapter. Epidemiological data may identify subpopulations at greater risk that may require targeted interventions in an effort at mitigation of the impact of the pandemic. A unique aspect of the influenza H1N1 pandemics of both 1918 and 2009 was their predilection to cause death in different age groups than is typical for influenza. While most seasonal influenza strains are most dangerous to the young and the elderly, these two hit healthy young adults more severely, as shown in Fig. 2. At a more mundane level, but equally important, vaccines are updated based on early surveillance data that detect strains currently in circulation.

At the global level, the World Health Organization (WHO) tracks influenza activity in a similar fashion. The Global Influenza Surveillance and Response System (GISRS) tracks influenza strains in active circulation globally from a virological surveillance approach. Geographical spread that assesses both intensity of influenza activity and active strains is tracked by WHO influenza transmission zones (Fig. 3) and reported biweekly. These transmission zones are distinct from WHO Regions. The former are geographical groups of countries, areas, or territories with similar influenza transmission patterns, while the latter are based on geopolitical characteristics.

The WHO categorizes pandemics into successive phases (Table 3). The phase indicates the extent of geographical spread, and not contagiousness of the pathogen, or severity of the disease.

This infrastructure focused specifically on the detection of influenza begs the question of surveillance for noninfluenza infections with pandemic potential. All of tools that are in place for tracking influenza are also effective in identifying other sources of systemic disease outbreak, including the clinical, epidemiological, and virological surveillance components. In addition, state and national health departments and ministries of health have in place statutory notifiable conditions (reportable diseases). By law, the clinical or laboratory detection, *or suspicion*, of these diseases must be reported to governmental health officials. These include specific known contagious pathogens as well as outbreaks of clinical syndromes, such as respiratory illness, diarrheal disease,

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Table 2 The CDC influenza surveillance system

Surveillance category	Report name and URL	Description
Virological	**FluView** https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html	Laboratory diagnosis based; also includes detailed virological investigations US WHO Collaborating Laboratories and NREVSS[a] Laboratories report the number tested, number positive, age group, and virus subtype each week A subset of isolates go to CDC for further characterization. This includes surveillance for novel influenza, i.e., human infections that differ from currently circulating viruses Does not include an indicator of severity of disease
Outpatient illness	**ILINet** https://gis.cdc.gov/grasp/fluview/main.html	Clinical diagnosis based 2,700 outpatient providers in all 50 states, the District of Columbia and the US Virgin Islands report the total number of patients seen, and number seen with influenza-like illness, by age group. This data set includes more than 30 million patient visits annually Does not include an indicator of severity of disease
Geographic spread	**State and Territorial Epidemiologists Report** https://gis.cdc.gov/grasp/fluview/FluView8.html	Laboratory-diagnosis-based State health departments report the estimated level of geographic spread of influenza activity in their states each week Does not include an indicator of severity of disease
Hospitalization	**FluSurv-Net** https://www.cdc.gov/flu/weekly/influenza-hospitalization-surveillance.htm	Population-based, laboratory confirmed, influenza-related hospitalizations in children and adults Covers over 80 counties in the 10 Emerging Infections Program states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and five additional states (IA, MI, OH, RI, and UT) An indicator of severity of disease
Mortality	**Pneumonia & Influenza Mortality Surveillance** https://gis.cdc.gov/grasp/fluview/mortality.html **Influenza-Associated Pediatric Mortality** https://gis.cdc.gov/GRASP/Fluview/PedFluDeath.html	ICD-10 diagnosis based (clinical and laboratory) The vital statistics offices of 122 cities across the US report weekly the total number of death certificates processed and the number for which pneumonia or influenza was listed as the underlying or contributing cause of death by age group. A rate of 1.645 standard deviations above the seasonal baseline is considered the "epidemic threshold" Influenza-associated death in children is a nationally notifiable condition. Demographic and clinical information are collected on each case A major indicator of severity of disease

[a]National Respiratory and Enteric Virus Surveillance System (NREVSS)

waterborne illness, and unexplained illness or death in humans or animals.

Response

Investigation

Once an unusual outbreak is detected, it is investigated and characterized. In the USA, investigation is generally initiated by local health officials and may be supplemented with federal assets. One of the primary federal assets is the Epidemiology Intelligence Service (EIS). These investigators are post-doctoral fellows and are part of a long-standing and globally recognized program. Disease detectives who investigate outbreaks, ready to deploy at a moment's notice, their field of operations covers the globe. Noteworthy past investigations are shown in Fig. 4.

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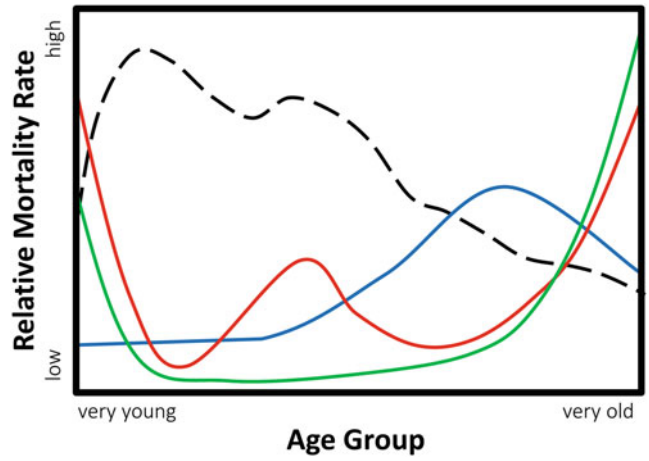


Fig. 2 Age-based influenza patterns. The dashed line indicates the typical relative incidence of clinical influenza by age, and solid lines indicate age-related mortality rates. Green illustrates typical seasonal flu mortality pattern, red is 1918 H1N1 influenza, and blue is 2009 H1N1

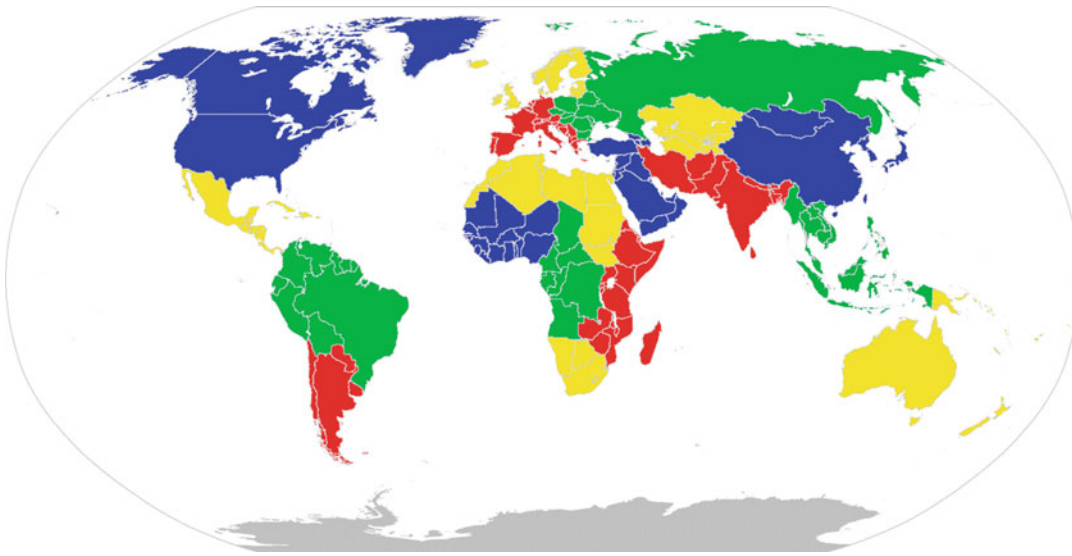


Fig. 3 WHO influenza transmission zones: North America, Central America – Caribbean, Tropical South America, Temperate South America, Northern Europe, Southwest Europe, Eastern Europe, North Africa, Western Africa, Middle Africa, Eastern Africa, South Africa, Central Asia, Western Asia, South Asia, Eastern Asia, Southeast Asia, and Oceana-Melanesia-Polynesia

Infrastructure and Organization

In the USA, national public health emergencies such as pandemics, like any other disaster, are managed under the National Response Framework (NRF): a comprehensive, national, all hazards approach to incident response, established by Homeland Security Presidential Directive 5 (HSPD-5) in 2003 and further refined in 2005 [4–6]. This plan is implemented by employing the elements of the National Incident Management System (NIMS) [7]. NIMS guides all levels of government and the private sector to work together by providing responders across the whole community with a shared vocabulary, systems, and processes. It defines an operational system that guides the ways in which personnel work together during a disaster, whatever its cause.

An important aspect of the NRF is the assumption that disaster events are managed best at the lowest possible geographical, organizational, and jurisdictional level. This means that the primary

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Table 3 WHO pandemic phases. Though specific to influenza, the general principles are applicable to pandemics due to other etiologies, such as coronavirus. Based on information from https://www.who.int/csr/disease/swineflu/phase/en/

Phase	Description
Inter-pandemic phase	
1	No viruses circulating in animals has caused disease in humans
2	An animal virus circulating among animals has caused disease in humans
Pandemic alert phase	
3	Some human-to-human transmission has occurred, but not at a level sufficient to sustain community-level outbreaks
4	Sustained human-to-human transmission leading to community-level outbreaks
5	Human-to-human spread of the virus into at least two countries in one WHO region
Pandemic phase	
6	Community level outbreaks in at least two WHO regions
Postpeak	Incidence decreasing below peak observed levels in most countries. Additional waves may occur
Postpandemic	Disease activity has returned to levels normally seen

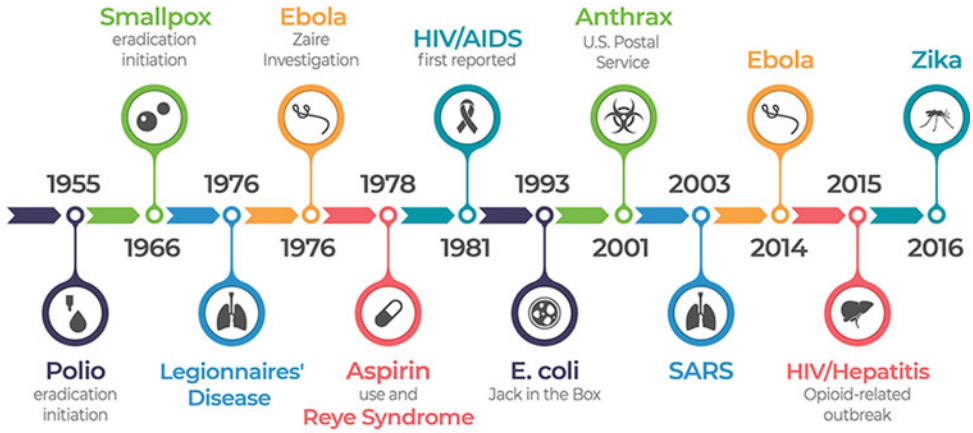


Fig. 4 Outbreaks investigated by the EIS. (Figure from CDC, public domain)

responsibility falls to local, state, and tribal governments. This is appropriate, as they are the first to respond and the last to leave – and for the local government, they *do not* leave. This level coordinates jurisdictional resources, exercises police or extraordinary powers as needed, and provides leadership of the response. They negotiate mutual aid agreements prior to the incident and request outside assistance when the local capabilities exceeded. Federal agencies advise and assist local response. In the USA, the Department of Homeland Security (DHS) is the principal agency for federal domestic incident management, coordinating federal resources when they are requested. All other federal departments may contribute, depending on the nature of the incident.

In addition to the command and control functions of NIMS, the NRF also requires tactical capabilities. These are organized as the Emergency Support Functions (ESF), listed in Table 4. An organizational structure that coordinates the resources and capabilities necessary to respond to a disaster, ESF, includes private sector capabilities of corporations and nongovernmental organizations, as well as state and federal capabilities. It is through ESF that the NRF endeavors to provide the support, resources, program implementation, and services that are most likely needed to save lives, protect property and the environment, restore essential services and critical infrastructure, and help victims and communities recover from a disaster.

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Table 4 Emergency support functions. Asterisks indicate those relevant in pandemic incidents

Designation	Description	Role
ESF1*	Transportation	Get what is needed to where it is needed
ESF2*	Communications	How to call for help, coordinate response
ESF3*	Public works and engineering	What about the infrastructure
ESF4	Firefighting	(self-explanatory)
ESF5*	Emergency management	Coordinating the response
ESF6*	Mass care, housing, and human services	Helping the victims
ESF7*	Resources support	The "stuff" that is needed
ESF8*	Public health and medical services	Addressing medical needs
ESF9*	Urban search and rescue	Finding the victims
ESF10*	Oil and hazardous materials response	Getting fuel; or cleaning the spill
ESF11*	Agriculture and natural resources	Food supply, materials
ESF12*	Energy	Powering the response; or dealing with a radiological incident
ESF13*	Public safety and security	Maintaining order
ESF14*	Long-term community recovery and mitigation	Rebuilding
ESF15*	External affairs	Coordinating across jurisdictions, specifically, internationally

Of special interest in pandemic incidents is ESF 8. In addition to local health professionals and health systems, there are state and federal resources that can supplement the medical response. Most states have a state emergency reserve of volunteers (SERV). These are databases of statewide health professionals who register and are credentialed in advance, in order to assist public health and healthcare systems in the event of an incident [8]. When a disaster strikes, these volunteers can be enlisted to help fill in the gaps where local healthcare systems are overwhelmed.

Table 5 lists key federal resources available to provide medical assistance in support of, and at the request of, state and local efforts. These resources include health professionals – full-time federal employees, a "reserve" force, and a volunteer force. Portable health care facilities and supplies for their operation are also part of this resource pool. Federal disaster resources *must be requested* by state officials; they are not deployed unilaterally. Not included in the table are military resources, which can augment and support the civilian resources of ESF8 (and most other ESFs).

The Strategic National Stockpile (SNS) is a collection of critical medications and supplies. While primarily designed to respond to military or terrorist attacks, when they would be rapidly dispensed through the affected state(s)'s official Points of Distribution, most of the constituent SNS parts have application to other types of disaster, including pandemics. The SNS can be used to facilitate the operation of the federal disaster personnel teams and facilities or it may be deployed to state and local responders independently of any other federal ESF8 resources. Figure 5 illustrates historical dispensing of the SNS.

Control Strategies

Stopping Versus Slowing the Spread

Following the detection of an outbreak with the potential of rapid spread, the initial goal is to prevent the spread completely. This is accomplished by quarantine of affected individuals until the disease has run its course or has been successfully treated. In addition, all precautions necessary are taken to prevent transmission of the disease to those who are providing care to the infected individual(s). When first established, the US Public Health Service was focused on identifying shipborne diseases and enforcing quarantine in order to prevent spread in the

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Table 5 Key federal sources of medical assistance. Additional details are at https://www.phe.gov/Preparedness/support/medicalassistance/Pages/default.aspx

Resource	Responsible authority	Description
Personnel resources		
Commissioned Corps, US Public Health Service [full-time federal employees]	Assistant Secretary for Health, Department of Health and Human Services	**Rapid deployment force.** Multidisciplinary teams capable of deploying within 12 h of notification to provide mass care at shelters, and staff points of distribution or casualty collection points **Applied public health teams.** Experts in public health that deploy within 36 h of notification and function as a "public health department in a box" **Mental health teams.** Behavioral health experts who can deploy within 36 h of notification and assess the affected population, responder stress, and provide therapy, counseling, and crisis intervention
National Disaster Medical System [intermittent federal employees]	Assistant Secretary for Preparedness and Response, Department of Health and Human Services	**Disaster medical assistance teams.** Multidisciplinary, capable of deploying within 6 h of notification to provide primary and acute care, triage of mass casualties, initial resuscitation and stabilization, advanced life support, and preparation for evacuation. Can sustain operations for 72 h without external support **Disaster mortuary operational response team**. Multidisciplinary team to recover, identify, and process deceased victims. May employ disaster portable morgue units to establish a stand-alone morgue operation **National Veterinary Response Team** provides assistance with veterinary services following major disasters, emergencies, public health, or other events **National Medical Response Team** provides medical care following a nuclear, biological, and/or chemical incident, mass casualty decontamination, medical triage, and medical care for stabilization for transportation
Medical Reserve Corps [volunteer responders]	Assistant Secretary for Health, Department of Health and Human Services	Provides the structure necessary to deploy volunteer medical and public health personnel in response to an emergency by identifying in advance specific, trained, credentialed personnel available and ready to respond to emergencies
Facility resources		
Federal Medical Stations	Assistant Secretary for Preparedness and Response, Department of Health and Human Services	A deployable healthcare facility to provide surge beds to support local healthcare systems. These are not mobile and cannot be relocated once established. Staffing is provided by displaced local/regional clinicians or can be provided by the federal government through any of the resources listed above. Supplies are from the Strategic National Stockpile
Material resources		
Strategic National Stockpile	Centers for Disease Control and Prevention	The national repository of antibiotics, chemical antidotes, antitoxins, ACLS medications, IV and airway supplies, ventilators, and other medical/surgical items. Organized by incident-specific "push-packs" that can be delivered to Federal Medical Stations or state points of distribution within 12 h of the decision to deploy them

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Fig. 5 Strategic national stockpile responses. (Figure from CDC, public domain)

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preantibiotic era. Even today, there are 20 Quarantine Stations strategically located at the US ports of entry where most international travelers arrive [9]. The idea of this strategy is analogous to quenching the spark before the flame begins. This strategy worked well in 2003 and 2014 for SARS and Ebola, respectively.

This primary strategy of prevention is reasonable when the number of infected individuals is relatively small and geographically localized. As the outbreak develops to an epidemic, this strategy becomes more difficult to effectively implement and ultimately may fail. Separation of infected from uninfected populations can be maintained to a degree, but when boundaries are political rather than geological, they tend to leak. The speed and convenience of modern modes of transportation further undermine efforts to contain the disease.

As an epidemic progresses to a pandemic, a different strategy is needed. Rather than *preventing* its spread – the goal is to *slow* its spread. This is the "flattening the curve" phrase, which became ubiquitous during the COVID-19 pandemic. While the same number of individuals will ultimately experience infection, the goal here is to avoid overwhelming the capabilities of the health system (Fig. 6), which would result in otherwise avoidable deaths. The slowing of the spread of the infection also has the potential to buy time for the development of improved treatments, and the deployment or possibly the development of a vaccine.

Slowing the infection presents some hazards in the case of a pandemic. By prematurely terminating transmission before a critical mass of protective seropositivity is reached in the population, the population could be left vulnerable to subsequent pandemic waves by the same organism – the disaster is not averted, it is merely postponed. The degree of population immunity, needed in the population to protect it, is dependent upon the reproduction rate (R_0, i.e., the number of new people infected by each infected person) of the infection. Once the reproduction rate passes below the "herd immunity threshold," where $R_0 \leq ((R_0–1)/R_0)$, incidence of the disease declines [10].

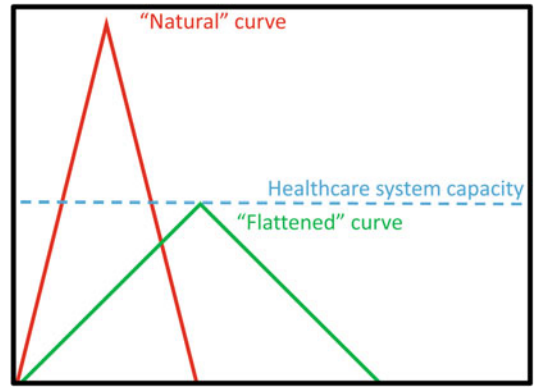


Fig. 6 Slowing transmission. The natural curve results in overwhelming healthcare systems and increase in otherwise avoidable morbidity and mortality. By "flattening the curve," while the same number of infections may occur, the healthcare system is not overwhelmed and thus is able to provide optimal care to all infected patients

There are a number of tools of use in slowing the spread of disease. Universal precautions, isolation procedures, environmental decontamination, and use of personal protective equipment such as gowns, gloves, masks, respirators, etc., by healthcare professionals while caring for infected or potentially infected individuals are important to prevent the spread of infection. Outside of the healthcare setting, the most aggressive tool to prevent contagion is quarantine, ranging from voluntary self-quarantine to legally enforced confinement. Less intrusive measures include "social distancing," which may vary from maintaining a minimum physical separation between individuals to avoiding mass gatherings to closing schools, businesses, and other enterprises. While the concept is intuitively sound, there is only limited evidence to suggest that social distancing is beneficial [11]. The implementation of barrier protection methods, such as face masks and gloves, by the general public is another strategy that has been employed, though currently evidence for patient-oriented outcomes is lacking [12].

Treatment

In spite of the best efforts at controlling the spread of a pandemic, clinical care of its victims will be

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needed. Perhaps the top priority is healthcare workforce protection – if this is neglected, the healthcare workforce will be rapidly rendered ineffective. Proper use of personal protective gear, isolation procedures, and environmental disinfection, although mentioned earlier, are worth repeating.

For familiar diseases without effective treatments, as well as those caused by novel pathogens, the most important care is supportive. Sepsis, shock, and respiratory (or other organ) failure, as well as other problems, need to be appropriately treated. When there are known specific treatments (e.g., antibiotics or antiviral medications with demonstrated efficacy against the pathogen), they should be used. For novel pathogens, or pandemics of familiar but untreatable diseases, there is a temptation to try a variety of unproven therapies. While the desire to "do something" is strong, it must be tempered. "Compassionate use" of unproven remedies may well be termed "compassionate harm" – every intervention has the potential to injure, and without data it is impossible to truly balance benefit against harm. This was seen in the early days of the COVID-19 pandemic, when any idea suggested was often widely adopted, usually without tracking outcomes [13]. *It is critical during pandemics that experimental interventions be monitored* for benefit and harm; properly controlled clinical trials are preferable *and possible* in these circumstances; at the very least, registries must be maintained for subsequent analysis of therapeutic effect.

In addition to pharmacotherapy, immunotherapy may be considered. Early in a pandemic, the use of convalescent serum may prove beneficial. Later, other therapeutic biologics based on protective antibodies may be developed. A protective vaccine to administer to uninfected individuals may become available, though a significant amount of time is required to demonstrate both effectiveness and safety. The first recipients of new vaccines should be those at highest risk of infection or severe disease, including healthcare workers. Sometimes, the immune response to the pathogen may be primarily responsible for the pathology, and immune system modulators may be worth considering. As with the caveat for investigational drugs, none of these interventions should be used without monitoring and tracking the results.

Perhaps, one of the most important lessons relevant to clinical care from the beginning of the COVID-19 pandemic was the importance of maintaining a broad differential diagnosis, and not overlooking the timely and appropriate care of *nonpandemic* disease. Common diseases are common, even during a pandemic, and neglect of acute and chronic diseases makes a sizeable contribution to the excess mortality that may be observed during a pandemic. While these deaths are decidedly a result of the pandemic, they are due to neglect and mismanagement, not infection!

Practice Preparedness

Key to a successful response to a pandemic, or any disaster, is preparedness. This was an important component of a Homeland Security Presidential Directive 8 which incorporated preparedness into the NSF [6]. Waiting until a disaster has arrived to prepare for it makes failure much more likely.

Caring for their regular patients is the principal professional obligation of the family physician in the event of a disaster [14]. However, without a plan for continuity, the physician's ability to aid their patients will be hampered. It is wise for the physician to ensure that a proper clinic disaster plan is in place, whether they are employed, volunteer, or in private practice. A written disaster plan is extremely valuable. The development of such a plan requires substantial thought and effort – and best done prior to a catastrophic event. It should integrate with the disaster plans of the local community, health systems, and the state/provincial governments [15–17].

One part of the disaster plan specific to pandemics addresses isolation measures. A simple example of the most basic of measures is separate waiting areas for patients with symptoms of infection and those with noninfectious illnesses. During the initial period of an outbreak, it may be necessary to temporarily postpone preventative health care, and take measures such as scheduling

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chronic disease management visits early in the day prior to scheduling patients with presumed infectious conditions, and other chronological isolation strategies. Many of these physical and chronological measures may be also beneficial during nondisaster periods, and during seasonal illnesses such as influenza. Following recent outbreaks and pandemics affecting the USA, there is increasing interest in incorporating negative pressure rooms into primary care clinic design.

Disaster planning should also address the requisitioning of personal protective equipment (PPE) and supplies. Healthcare professionals are much more reluctant to care for disaster victims when adequate PPE is not available [18]. Because of the potential for resupply system disruption, PPE and all other material required for clinic operation should be stockpiled in adequate quantities to continue clinic operations for an extended period. This includes adequate water, food, and even shelter space for clinic staff while at work, depending on the potential level of disruption of local infrastructure caused by the event.

During a pandemic, some clinic staff will be unable to perform their functions due to personal illness, caring for family members, disruption of the local transportation system, fear of illness, or other reasons. Cross-training staff to perform functions outside their usual job description can help compensate for staff absenteeism.

A communications plan is critical. How will the physician communicate with his or her staff following the disaster? How will patients communicate with the clinic? How will the physician communicate with public health authorities? How about with the rest of the community?

Finally, the plan needs to address one of the most ironic situations in a pandemic: *health* care professional job loss and facility closure during a public *health* crisis. Due to social distancing and other isolation strategies, as well as fear of acquiring infection in a healthcare facility, patient visits have the potential to drop precipitously. This can result in the need to lay off staff, significant loss of billing-indexed physician income, and even practice closure. While it is difficult to fully anticipate and mitigate the economic impact of a pandemic on a family medicine practice, steps can be taken to soften the blow. Potential strategies include actions such as increasing the use of telemedicine, retasking clinic staff to jobs such as quality improvement activities and chronic disease registry creation and maintenance when direct patient care duties decrease, encouraging employees to utilize their paid time off during the lulls in clinic activity, and transitioning physicians and other staff into the "surge labor pool" of the local or regional hospitals during the crisis.

Opportunities in the Broader Response

Family physicians have a uniquely comprehensive clinical skill set that is not limited by patient age or sex, organ system, or disease state. It encompasses procedural and cognitive proficiencies, flavored by a public health/community health orientation. This can be of great value outside of their local practice in times of crisis such as pandemics and other disasters. All family physicians should give serious consideration to registering with their state's SERV. For some who are looking for a higher level of involvement, volunteering through NGOs or federal avenues such as the Medical Reserve Corps, intermittent employment with National Disaster Management System, or even a career focus in the Commissioned Corps is a possibility. The key is to establish the connections *prior to* the next disaster.

Ethical Considerations

Though the final section of this chapter, the ethics of pandemics are of primary importance. The countless ethical issues involved in medical care under ordinary circumstances are relevant; there are two that warrant extra discussion here.

Outbreaks, epidemics, and pandemics are particularly dangerous times for healthcare professionals. What is the moral duty to treat patients during these times? During the 2014 Ebola outbreak, 95% of expatriate doctors left Liberia – just when they were needed the most [19]. Similarly, in the early days of the AIDS pandemic, many

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physicians refused to treat AIDS patients, prompting a soul-searching discussion in the medical profession [20]. Historically, many physicians fled cities during the plague, including Galen from Rome and Sydenham from London. Prominent physicians fled Philadelphia and New York during outbreaks of yellow fever and cholera in the eighteenth and nineteenth centuries. Many physicians who did not leave refused to visit patients who were acutely ill. However, most physicians treated patients who sought help [20]. The ethical principles of beneficence and justice compel one to ask, "Did we enter the profession to help those suffering? Or make a comfortable living off of the suffering (so long as risks are relatively low)?" Family physicians have a clear track record of selecting their specialty, not for financial gain, prestige and respect, or a comfortable lifestyle – indeed, often in spite of the opposite – but to make a meaningful difference in the lives of their patients and communities. When responding to this ethical call, workforce protection is critical: good isolation practices, adequate PPE, and supporting one another to avoid critical incident stress and burnout [21].

The WHO defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity [22]." This clearly specifies health and disease as reaching far beyond a merely biological perspective. The social determinants of health are increasingly receiving proper attention within the US health care delivery systems. In responding to the threat of a pandemic, it is vital that this continues. Strict quarantine-like activities significantly impact education, mental health, and the economy. This impact is disproportionately felt by those most disadvantaged by social determinants of health, hurting those most vulnerable. The excess mortality seen during pandemics is the result of chronic disease neglect, domestic violence, suicide, food insecurity, etc. – not just the direct biological result of infection. An exclusively biological approach inevitably violates the principles of autonomy, justice, and nonmaleficence. The big picture of health that encompasses all its determinants is what Family Medicine is all about. Its voice must be heard advocating for patients and a balanced approach to society's pandemic response.

Box 1 Incident Command (ICS) for Health Professionals

Excerpts from "Incident Command System Primer for Public Health and Medical Professionals," US Department of Health and Human Services [28].

Traditionally, preparedness actions for public health and medical emergency or disaster response have focused on the operational (tactical) knowledge and skills required by individuals to respond. This has resulted in training programs developed primarily for such topics as victim triage or the characteristics of specific hazards (e.g., chemical or biological agents). Though this knowledge is important and has relevance, much of it is easily accessed during incident response and does little to maximize the capacities and capabilities of existing structures. In other words, teaching and training on these topics provides little in the way of strategic knowledge that improves the ability of individuals to respond as part of a cohesive system. . .

Public health and medical disciplines have focused historically on the operation functions necessary for response. Experience demonstrates that problems will arise if inadequate attention is paid to the other functional areas:

- Protection of responders: Inadequate initial consideration for personal protective equipment (PPE) could cause responders to be exposed to an infectious disease (a safety function).
- Management of strategies: Inadequate coordination of strategies and tactics for screening for a disease might promote confusion in the patient population if people receive different evaluation or treatment at various healthcare facilities (a command function).

(continued)

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Box 1 Incident Command (ICS) for Health Professionals (continued)

- Management of information: Inadequate information management might result in the transportation of patients to a hospital that is already overwhelmed with walk-in patients (a planning function).

Many of the most severe challenges during an incident response arise within the response system itself. Therefore, ICS devotes a large portion of its activities to supporting the response system, whether through logistics, planning, or administration/finance sections. . .

For public health and medicine to be considered equal partners and fully integrated into the response community, the concepts put forth in ICS should form the basis of their response systems. Without this foundation, it will become increasingly difficult for public health and medicine to maximize their roles in incident response.

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Part X

Environmental and Occupational Health Problems

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Occupational Health Care

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General Approach to the Treatment of the Worker 631

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Introduction

The evaluation and management of work-related health conditions offers the family physician a unique medical challenge that may extend far beyond the confines of a clinic or a hospital. The floors of a lumber mill, the flight deck of a 747, and the dark tunnels of a coal mine are but a few of the environments that can become the concern of the family physician caring for the worker.

From Antiquity to Nanotechnology

The practice of occupational and environmental medicine has its roots in antiquity. Concern for the health of workers has been documented as early as ancient Egypt when Imhotep, considered the grandfather of occupational medicine, described treatment for injuries sustained by pyramid workers. Similar writings are found in ancient Greece, when both Hippocrates and Pliny the Elder wrote on the maladies of miners, horsemen, and metalworkers. Throughout history, many figures have advanced the health of workers. However, it is Bernardino Ramazzini that is considered the "father" of modern occupational medicine. Through his dedication to exploring the ailments of the worker, Ramazzini expanded the breadth and depth of occupational medicine by promoting worksite visits. The toils of his studies resulted in one of the earliest textbooks of occupational medicine, De Morbis Artificum Diatriba, which was published in 1700 [1].

Since the time of Ramazzini, there have been many pioneers of the specialty. One more modern contemporary that deserves special attention is Dr. Alice Hamilton. In the early 1900s, Hamilton not only advanced our understanding of the toxicological dangers of work, such as lead, but she also championed the importance of workplace safety. Hamilton's work and accomplishments extend far beyond the care of workers; she was a prominent social activist and also the first female faculty member of Harvard University [2].

Over the last two decades, the most important change in occupational medicine has been a focus on the importance of work. In the past, there was great emphasis in ensuring people were fit for work, leading to the exclusion of disabled persons from the productive work they desired. Moreover, a large part of treating work-related injury and disease was removal from work on medical grounds. Although this may be still necessary in some cases, it is now recognized that work is crucial for health, socialization, and personal identity. Conversely, absence from work is frequently demotivating, demoralizing, and fraught with risks of depression, adverse mood changes, deleterious effects on career progression, and iatrogenically induced prolonged/permanent disability. Poor outcomes have also been demonstrated in occupational injuries compared with similar injuries sustained from sport and recreation.

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These considerations have led to a revised approach to work injuries. Occupational medicine is now focused on maintaining functional ability by returning injured workers to productive employment via appropriate work restrictions matching the job to the worker, [3] and case management. It is in this endeavor that occupational medicine finds itself at a frontier within the practice of medicine.

The blossoming concept of work as a potential healing entity, coupled with the development of novel compounds and industries that may represent dangers to health that have not yet been fully delineated, such as graphene and nanotechnology, presents ongoing health challenges for workers and occupational medicine providers.

This chapter will discuss the epidemiology of work-related illnesses and injuries, the history of the origins of Occupational Medicine in the United States as a well as review some common occupational diagnoses, in no particular order of importance. The diagnoses discussed are in no way exhaustive.

Practice Overview

At the level of the individual patient, occupational and environmental medicine (OEM) focuses on the care of the injured worker, the prevention of workplace injury and illness, and the improvement of worker health and productivity. A division of preventive medicine, OEM is one of the smallest medical specialties recognized by the American Board of Medical Specialties. However, the expertise OEM provides regarding worker health and population management skills renders it an increasingly important specialty.

Despite this need, there is a shortage of OEM physicians. Indeed, in 2018, only 71 physicians achieved board certification in OEM [4]. In addition, with the number of board-certified occupational medicine specialists in decline, it is anticipated that nearly 1700 OEM physicians will retire in the next 10 years. The result is that there will be a 33% reduction in specialist numbers [5]. As such, there is a burgeoning practice opportunity for family physicians that are willing to pursue additional training and education in the treatment of workers.

Epidemiology

As the number of specialist OEM physicians declines, the incidence of work-related health conditions continues to be significant. In 2018, there were approximately three million nonfatal workplace injuries and illnesses reported in private and public sectors. Alarmingly, 2018 was the first year the rate of total recordable injuries did not decline since 2012. More than half of these were injuries severe enough to require work modifications, job transfer, or time off from work [5]. For the private sector, the highest rates occurred in the manufacturing, health care, and retail industries. For state and local governments, which historically have had higher incidence rates than the private sector, nursing and residential care facilities have the highest rates of injuries and illnesses. Agriculture, forestry, and fishing experienced the highest fatality rates. In all sectors, persons 55–64 years of age had the highest incidence of injuries (113.4/10,000). The most common type of injury events were overexertion and bodily reactions, slips and falls, and contact with objects. The most common injuries were sprains/strains/tears, soreness/pain, and cuts/lacerations/punctures [6].

While rarely considered during national debates over the financing of medicine, the direct cost associated with work-related health care is tremendous. In 2018, the cost of worker's compensation-related health care was approximately 170.8 billion dollars [7] split nearly evenly between medical and indemnity costs [7]. In addition, injuries in 2018 resulted in roughly 70 million lost workdays. These costs are staggering, especially when compared to the 2015 cost (in millions) for heart disease (113), trauma (102), and mental disorders (98) [8]. Moreover, the true costs of occupational injuries and disease are much larger when indirect costs of lost productivity are included. The loss of productivity exceeds the direct costs of diagnosis, treatment, and indemnity payments (wage replacement while off work) for injured workers.

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While these data increasingly provide incentives for employers to prevent work-related injury and disease, much of society remains unaware of the cost of injured workers.

Legal Underpinnings and Entities

Given that work is an integral part of the lives many of the patients that family physicians will see and work may affect their presentation of illness or injury, a basic understanding of the key regulatory bodies and systems is necessary for successful practice and delivery of care.

Worker's Compensation (WC)

WC is the oldest form of social insurance in the United States and the third largest source of support for disabled workers after Social Security and Medicare. Workers' compensation allows for the provision of monetary compensation for medical and rehabilitation costs and lost wages to certain workers with work-related injuries or disabilities. Prior to the establishment of WC, litigation was usually necessary for full compensation. Workers rendered injured or ill due to a work-related injury or illness bore the full brunt of medical care and lost wages unless employers voluntarily offered compensation. Founded on the principle of providing a compulsory "no-fault" form of insurance for workers injured in the course of employment, employers are held responsible for compensation for work-related injuries and illnesses, regardless of findings of cause, through an insurance mechanism. In this no-fault system, in exchange for certain and prompt compensation, the worker accepts compensation limited to the standard amount specified by each state, whether the payment fully covers lost wages, pain, and/or suffering. As such, WC is the exclusive remedy for injured workers.

The first workers' compensation laws were passed in 1911 by nine states, with Hawaii being the last state to do so in 1963. A similar system had already existed in Europe with Germany being the first to pass these laws in 1884. While WC laws are similar overall, differences can exist between states and federal and private entities. It is important for the family physician to be aware of this and familiar with the nuances of their local jurisdictions [1].

Occupational Health and Safety Administration

At the turn of the twentieth century, industrial accidents in the workplace became more publicized, causing public outrage. In the wake of disasters such as the Triangle Shirtwaist Factory fire, regulatory agencies and acts, such as the Safety Appliance Act and the United States Bureau of Mines were formed. With further increases in industrialization that followed World War II, the incidence of workplace injuries increased dramatically. The dangers of industrialization were compounded by the increasing use of industrial chemicals, many of which had unknown health effects. It is estimated that in 1970, there were 14,000 work-related fatalities in the United States [9].

In 1970, the US government passed the bipartisan Occupational Safety and Health Act (OSH Act), the purpose of which was to create and maintain the safety and health of workers in the United States through training, education, and assistance. Perhaps, the most powerful component of the act is its general duty clause, which states each employer:

> shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees.

The clause enables the broad protection of workers and workplace safety, even in the absence of specific applicable regulations or standards.

The act led to the establishment of the most recognized government agency pertaining to work safety, the Occupational Health and Safety Administration (OSHA). OSHA, a component of the Department of Labor, is the government's regulatory agency for work safety. Some of the

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agency's many services include regulatory inspections and enforcement of standards, such as those pertaining to lead and blood-borne pathogens [10].

National Institute of Occupational Safety and Health

The OSH Act also created the National Institute for Occupational Safety and Health (NIOSH) as part of the Centers for Disease Control and Prevention. The purpose of NIOSH is to conduct research on worker injury/illness and to make recommendations on workplace safety issues. Examples of NIOSH's research areas include such subjects as the danger of antineoplastic medications to health-care workers and hazards in offshore gas/oil extraction. In addition, NIOSH also funds education, research, and training in occupational health. The roles of NIOSH and OSHA are distinct, with OSHA being the regulatory aspect of work safety [11].

Americans with Disabilities Act (ADA)

The purpose of the ADA, promoted in 1990 by Senator Tom Harkin of Indiana, is to prevent discrimination against individuals with disabilities in transportation, public accommodations, communications, governmental activities, and employment [12]. The ADA was one of the most important pieces of social legislation in the United States and represented a major change in thinking. An impetus to the act was the ongoing exclusion from employment of many Americans with disabilities or a history of disabilities, even when such individuals had improved medically and/or wished to work. The act was amended in 2008 by the Americans with Disabilities Act Amendment Act (ADAAA).

A complete understanding of the nuances of this complicated piece of legislation is beyond the scope of this chapter. However, a basic understanding of ADAAA by the family physician is important as they may be called upon to opine on the physical capabilities of workers.

First, private employers with greater than 15 employees, state/local governments, employment agencies, and labor unions must provide accommodations for applicants and workers with disabilities if such accommodations would not impose undue hardships on the employer. Examples of accommodations include alteration of work schedules and the use of modified equipment. Undue hardship is defined generally as "an action requiring significant difficulty or expense," when considering the applicable covered employer's situation.

Second, the act prevents pre-hire inquiries, such as physical examinations, into an applicant's medical status. However, an employer may require a physical examination to determine if an individual can perform the essential functions of a job after an offer of hire has been made and before employment commences. Such examinations must be required of all employees and not on an individual basis. Pertinent records must be kept confidential and separate from employee human resources files [13].

Family and Medical Leave Act (FMLA)

FMLA was passed into law in 1993. The purpose of this law is to provide employees 12 weeks of unpaid, job-protected leave for qualified medical conditions. In addition, health insurance benefits as part of employment must be continued during such leave. FMLA is applicable to all public agencies, public and private elementary/secondary schools, and employers with greater than 50 employees. To qualify for FMLA, employees must have worked for an employer for 12 months, worked 1250 hours in those 12 months, and worked in a location where the company has greater than 50 employees within a 75-mile radius. Qualifying reasons for leave include the birth/care of a newborn, the initiation of foster care/adoption by the employee, the care of a family member with serious medical conditions, or a serious medical condition of the employee that prevents work [14].

Many family physicians encounter this piece of legislation as a multipage form with a request

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from patients for physician certification. Satisfactory completion of this documentation will allow appropriate protections for both the patient and employer and efficient execution of this law.

General Approach to the Evaluation of the Worker

The evaluation of the worker requires considerations and elements that extend beyond normal history and physical examination.

The Standard for Documentation

The provision of occupational health services occurs in a legal framework. The family physician should assume that any records pertaining to a work-related health condition will be scrutinized by numerous stakeholders, including insurance adjusters, employers, and legal representatives. For example, claims adjusters require detailed information in order to appropriately manage a worker's compensation claim. A failure to provide precise documentation can lead to a loss of appropriate medical treatment covered by workers compensation, costly delays in care, and erroneous assignment of financial/legal responsibilities [15]. As such, attention to detail and accuracy is required throughout occupational health care. It would not be overdramatic to state that if scalpels are the tools of the surgeon, the instruments of the successful occupational health provider are words.

The Systematic Injury History

The majority of occupational health-related treatment by the family physician involves the care of an acutely injured worker. Among the most common work-related injuries seen in primary care clinics involves low back pain, and this complaint can be used to demonstrate the proper documentation of a potentially injurious work event.

Certainly, it would not be sufficient to simply document a "patient injured while lifting at work." Legal needs aside, such a vague description sheds little insight into neither the diagnosis nor avenues for preventing recurrences. Similar to a forensic investigation, any report of a potentially work-related injury should include the mechanism of injury, the location, the time of the event, and the employees involved in the event. A useful paradigm for recalling these crucial elements is the "4 Ws": what, when, where, and who.

Medications and Substances

Outside of the obvious dangers of alcohol and illicit drug use at work, several legal medications can be hazardous. For example, in 2018, there were roughly 67,000 deaths from drug overdose. Seventy percent of these deaths were due to prescription opioids [16]. Both prescription and over the counter medications can potentially cause serious and dangerous impairment of workers on the job. Because of this, a detailed description of a worker's medication regimen is required for those who have suffered an acute injury. Special attention should be paid to dosing schedules. For example, a potentially sedating medication, such as cyclobenzaprine (Amrix, Fexmid, Flexeril), may not pose a work safety issue if the employee only works day shifts and the medication is taken in the evening.

An Objective Physical Examination

The physical examination of the worker differs from general primary care in one crucial way: an emphasis on objective evidence. Insurers are conscious of the possibility of fraud, and thus, there is a strong desire to limit liability for non-work-related conditions. Consequently, insurers place an emphasis on objective indications of pathology. The family physician should note as many objective indications of pathology, such as straight-leg tests and reflexes, as possible during

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the examination. Indications of nonorganic etiologies should also be noted. It is important to note that the pursuit of objective evidence does not discount the report of subjective symptoms by patients. Some legitimate and serious medical conditions, such as migraine headaches, have no objective signs on examination.

The Occupational History

Understanding the nature of a patient's work is vital for the treatment and management of work-related medical conditions. US physicians rarely inquire about work activities during routine clinical encounters [17]. This finding is unfortunate as family physicians are frequently the first physicians to evaluate work-related diseases.

The occupational history need not be an overly tedious and lengthy task [18]. In the case of a simple injury, only a brief history of pertinent facts may suffice. For more complicated diagnoses, such as an occupational infection or chemical injury, more detail may be required. Obtaining the occupational history can be expedited by having patients complete an occupational history questionnaire prior to the clinical visit.

An occupational history begins with obtaining basic information such as job title, employer, work schedule, and general work activities, in particular the activities surrounding the presenting injury or illness in some cases. Special attention should be given to any recent changes at work, such as new equipment/chemicals or alterations in work schedule. It should be noted that a simple description of the current job and tasks is may be insufficient when evaluating workers with ailments. Some exposures, such as asbestos, can take several decades to produce health effects. Thus, a review of a patient's entire work history may be necessary in some instances. The establishment of whether the injury or illness is work-related is important in that removing the exposure may potentially help the condition at hand. Additionally, this ascertainment will help determine the payor [19].

Psychosocial Factors

The complicated interplay between work, health, legal entanglements, and worker's compensation demands a careful assessment of psychosocial factors when caring for workers. For example, psychiatric conditions are associated with maladaptive coping mechanisms and delayed recovery from work-related low back pain [20]. The family physician should assess for psychosocial factors, such as work monotony, relationship with supervisors, and job satisfaction. The purpose of inquiring about such stressors is not to discredit the patient or to imply malingering. Rather, identifying such complications can provide additional treatment options, such as pain counseling or depression treatment, and help to identify and remove otherwise seemingly insurmountable barriers for recovery and return to work [21].

General Approach to the Treatment of the Worker

Communication

Occupational health care can be a challenging endeavor for the family physician. Such emotions are compounded for the patient, many of whom have significant home, work, and financial stressors in addition to the medical condition. Uncertainty, such as with diagnosis and return to work, has been linked to poor recovery and outcomes with work-related care [22]. Unchecked catastrophizing by the worker has been shown to impede improvement [23]. Thus, thorough and clear communication, with a plan for improving function and symptoms, by the physician is of paramount importance. For example, setting return to work dates and educating workers on how to prevent reinjury and recurrence can promote early RTW [24]. Catastrophizing can be mitigated by giving proper context to injuries and diagnostic findings and by positive reinforcement regarding the ability of the worker to perform their job duties. Using modified duty/light

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duty titration to progress the worker toward full duty by allowing them to remain in the workplace, surrounded by the culture of work, can help toward successful maintaining of work status and return to work.

Medications

In occupational injuries, the physician is also repeatedly tasked with managing pain. Unfortunately, the increasing use of opioids for the treatment of non-cancer-related pain has led to a greater potential for injured workers to be using impairing medications while at work. In the interest of the worker and the public, the family physician treating work-related pain should minimize the use of impairing medications, such as opioids and muscle relaxers. This is especially true for what are called "safety-sensitive" work positions. A systematic review of nearly 22,000 studies by ACOEM found a positive association between opioid use and motor vehicle crashes. Based on this, ACOEM now recommends that workers performing safety sensitive work, such as commercial driving or crane operations, should not use opioids acutely or chronically [25]. Early use of opioids for the treatment of acute, work-related low back pain has been shown to be associated with prolonged disability, higher medical costs, and prolonged opioid use. Much pain from occupational injuries can be effectively managed with acetaminophen and nonsteroidal anti-inflammatories [26].

Return to Work

One of the most important ways the family physician can serve the best interest of the worker is with appropriate management of return to work. Many physicians inappropriately assign time off from work for injured patients. One of the primary reasons for this is a perceived duty to be a patient advocate. Family physicians, like other medical providers, are motivated by a desire to minimize suffering and pain. Thus, when a worker complains of pain at work, removal from work appears to be in the patient's best interest. However, it is the converse that is usually true. It has been showed repeatedly that work, in safe environments and with proper guidance, is of paramount importance to health. Removal from work is associated not just with financial loss but also increased mortality from cardiovascular-, respiratory-, violence-, alcohol-, and accident-related etiologies [27]. Likewise, continued work maintains physical and mental conditioning. Thus, it is the return to work as safely and as soon as possible that is almost always in the worker's best interest. This endeavor should be the goal of the family physician's advocacy.

Appropriate return to work can also be adversely affected by the time constraints of the busy family physician's schedule. Time limitations are in turn compounded by a lack of training in return to work by most medical providers outside of occupational medicine. To improve the efficiency of return to work discussions, ACOEM and the American Medical Association (AMA) have created guidance documents for return to work recommendations by primary care physicians [28]. One of the unifying features of the guidelines is the use of a step-based algorithm [29].

The proper use of the algorithms is dependent on having a sound understanding of the definitions of restrictions, limitations, and tolerance [30]. Restrictions are activities that a worker should not perform due to personal risk or risk of hurting others. Limitations are needed when there is a task the worker cannot perform due to their medical condition. Tolerance is the ability of the worker to endure symptoms. It is important to remember that tolerance cannot be determined reliably by medical science. Ultimately, it is the worker that decides to tolerate symptoms that do not cause worse injury or pose a danger to self/others [29].

Removing a worker from work without considering activities the worker can perform within the context of work or even working full duty with the presenting injury is a disservice to the worker and to society. The family physician should try to gain an understanding of the job tasks and direct the worker/patient accordingly.

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Representative Occupational Medicine Challenges

Conditions: Musculoskeletal Injuries

Musculoskeletal injuries represent the bulk of work-related medical conditions encountered by most physicians. In a survey of family physicians between 1997 and 2000, 56% of work-related care by family physicians involved acute problems, and 48% involved musculoskeletal chief complaints [31]. In 2018, the incidence of musculoskeletal disorders was 27.2 per 10,000 workers. Sprains, strains, and tears were most common types of injuries by far.

The treatment of many common industrial injuries is covered elsewhere in this text. Table 1 summarizes a few of the work-related injuries most frequently seen by family physicians and lists their potential risk factors.

Conditions: Infectious Exposures

Exposure to infectious agents at work is a risk faced by many industries. This risk is especially robust in health-care-related fields, and the family physician can expect to encounter work-related infectious exposures, even if the provider is not actively providing occupational health-care services. An estimated 5.6 million workers are at risk from blood-borne pathogens. Between 1995 and 2007, there were 30,945 exposure events in the National Healthcare Safety Network. Eighty-two percent involved percutaneous injuries and 79% percent involved blood products. Nurses and providers were the most frequently injured, involved in 72% of cases [36, 39].

By far, the most concerning health-care-work-related infections are HIV, hepatitis B, and hepatitis C. The potential impact of these infections in the health-care workforce is so great; the subject is addressed specifically by the OSHA Bloodborne Pathogen Standard (29 CFR 1910.1030). To prevent unnecessary transmission of blood-borne pathogens, the CDC provides in-depth and updated postexposure management protocols on their website. Management options can include rapid initiation of antiretrovirals for confirmed HIV exposures and the use of the hepatitis B immunoglobulin/hepatitis B vaccine for hepatitis B exposures. Unfortunately, there is no post-exposure treatment for hepatitis C other than monitoring.

While these viruses have remained the primary blood-borne pathogen concerns for health-care workers, there are several other infectious agents not involving blood exposures that can be encountered in the workplace. There is perhaps no better example of the havoc that infectious diseases can

Table 1 Common work-related musculoskeletal injuries/conditions seen by family physicians and relevant risk factors

Condition	Potential occupational risk factors	Nonoccupational risk factors
Low back injury [32, 33, 34]	Repetitive loading of spine Inadequate rest time at work Awkward lifting Lack of decision control High job demand/stress	Psychiatric disorders Age Smoking
Carpal tunnel syndrome [34–36]	High hand force Prolonged hand force Vibration Repetitive motion	Diabetes Pregnancy Hypothyroidism genetic predisposition
Rotator cuff tear [34, 37]	Prolonged shoulder flexion Forceful pinching Work above at or above shoulder height Work stress	Age Overhead sports
Slips and falls [38]	Weather Poor lighting Slippery surfaces	Inappropriate footwear Age Fatigue

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create in the workplace than the 2020 COVID-19 pandemic. After the initiation of social distancing during the pandemic, the task of managing workplace and community exposures to the novel coronavirus, work restrictions, and the development of testing algorithms fell squarely on the shoulders of occupational health. The scale of the social isolation and quarantine efforts was unparalleled in modern times and management required the cooperation between occupational medicine and virtually every other field of medicine. Although COVID-19 is an extreme example, infections such as tuberculosis, pediculosis, scabies, and pertussis represent more typical challenges. The management of each of these conditions is outside the scope of this chapter, and the family physician interested in managing community exposures is encouraged to review materials from the CDC and to interact with local occupational medicine providers and emergency management systems.

Finally, zoonotic infections can also pose serious risks for some workers. Table 2 summarizes some of the zoonotic illness and their associated occupations and settings.

Conditions: Chemical and Environmental Exposures

The EPA's catalog of chemicals used at one time or another in industry exceeds 80,000. Most recently, the EPA estimates that 7500 chemicals were used by industry in 2012 [40]. Many such chemicals can result in serious health effects, including cancer and death. Similarly, both indoor and outdoor environments can produce symptoms and illness, even in the absence of harmful chemicals or chemical concentrations. Table 3 summarizes some of the most well established chemically and environmentally induced health conditions.

The chemical and environmental exposures most commonly encountered by the family physician are limited to a few conditions. The most prevalent are occupational skin diseases, building-related illness, and occupational respiratory conditions.

Latex Allergy

To meet compliance with the Bloodborne Pathogen Standard, which required barrier methods during health-care delivery, the use of latex gloves increased dramatically. This resulted in an increase in immediate hypersensitivity reactions associated with an IgE type I response to naturally occurring rubber from the *Hevea brasiliensis* tree. Those at risk include health-care workers food handlers, security personnel, and emergency service personnel (i.e., paramedics) [41]. Atopy is an independent risk factor. Rates of latex allergy have decreased in recent years with changes in latex processing and the increased use of latex free gloves [42, 43].

Symptoms from latex allergy can range from simple urticaria to life-threatening anaphylaxis. Symptoms typically begin within a few minutes to an hour of contact. Inhaled exposure can occur in the presence of powdered latex. The diagnosis is confirmed by skin prick testing or RAST testing for specific IgE. The primary strategy for management is avoidance.

Building-Related Illness

With increased focus on the safety of work environments in recent years, concerns and symptoms related to indoor air quality are becoming more common. There are several terms that describe conditions secondary to indoor air quality, such as "sick building syndrome" (SBS), more recently referred to as building-associated illness (BAI), and multiple chemical sensitivity [44]. It may also be referred to as idiopathic environmental intolerance (IEI). All of these conditions can lead to a vague constellation of symptoms, such as headache, upper respiratory symptoms, and fatigue. While abnormalities in specific components of indoor air quality (IAQ) can be the cause of such complaints, symptoms are often reported in environments where IAQ is within normal limit, often other than increased carbon dioxide levels, indicative of a mismatch between airflow and human occupancy. Although some consider many instances to be psychogenic, indoor air contaminants below the irritation threshold concentration can cause symptoms, especially those with low odor thresholds.

Several factors can contribute to poor indoor air quality. Environmental elements to consider are building ventilation rates, temperature and

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Table 2 Unique occupational infections, symptoms, and associated work and environments

Condition	At risk occupations/environments	History/pearls
Brucellosis	Veterinarians Exposure to fluids and aborted products of conception from infected livestock consumption of products from infected livestock, such as unpasteurized cheese/milk Laboratory personnel, via aerosolization Slaughterhouse workers Recent international travel	Undulant fever with sweats and malaise Systemic involvement Can be detected via antibodies and treated with antibiotics
Rabies	Animal bites, especially bats Biologists, veterinarians Greenhouse workers	Postexposure treatment can consist of rabies immunoglobulin and active vaccine Consider preexposure prophylaxis in those working with animals, especially in endemic areas abroad
Q fever	Veterinarians Animal caretakers Farm workers, especially those working with sheep, cattle, and goats Living downwind from contaminated farms or farm products (i.e., manure, dust) Laboratory personnel	Caused by Coxiella burnetii Exposure is typically through products of conception, fluids, or dust Extremely resistant to environment Widely variant clinic presentation, including flu-like illness, hepatitis, pyrexia of unknown origin, and pneumonia Liver function tests may be elevated in many patients
Scabies	Health-care workers Spread via direct skin to skin contact with Infected individuals Higher risk in crowded environments, such as nursing homes or correctional facilities	Caused by human itch mite, *Sarcoptes scabiei* Intense itching and rash Can be spread from an asymptomatic carrier Usually no symptoms for 2–6 weeks
Leptospirosis	Farmers, ranchers, veterinarians, sewer workers, rice farms, laboratory personnel, and loggers Spread in urine of farm animals Higher incidence in tropical regions Exposure occurs via contaminated soils or Animal tissue/urine Subsistence farming and urban slums Flooding associated with disease outbreaks	Caused by spirochetes from the genus *Leptospira* Varying clinical presentation, from subclinical to death Usually fever, myalgias, headaches, cough, nausea, and vomiting Look for conjunctival suffusion
Tularemia	Laboratory personnel Farmers Veterinarians Hunters Landscapers Meat handlers Animal or insect bites, especially ticks	Caused by *Francisella tularensis* Ocular and aerosolized exposure also possible Can survive long term in adverse water conditions Nonspecific symptoms, usually a combination of Fever, malaise, and anorexia fever may be intermittent
Rat-bite fever	Laboratory personnel Pet shop workers	Caused mostly by *Streptobacillus moniliformis* Exposure via bites/scratches or fecal contaminated food Clinical course varies depending on infectious agent

References [34, 45, 46]

temperature fluctuations, humidity, chemicals (i.e., formaldehyde and ozone), and odors. Personal factors, such as atopy and contact lens use, and psychosocial factors should also be considered.

As building-related illnesses can involve significant anxiety, clear and open communication is important to effective management. Initial evaluation begins with an interview of affected

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Table 3 Chemicals/elements and associated health conditions

Chemical/ elements	At-risk occupations/environments	History/pearls
Asbestos	Construction Shipbuilding Insulators Environmental contamination	Lung cancer Mesothelioma Pathology can develop many years after exposure Malignancy risk significantly increased with smoking
Silica	Sandblasters Concrete/masonry workers Mining	Chronic obstructive pulmonary disorder Scleroderma Increases risk of tuberculosis Unlike coal, causes calcification of hilar lymph nodes
Coal	Coal miners, especially those at the drilling face or with other heavy dust exposures	Lung fibrosis Unlike silicosis, no increase in TB or fungal infections in simple cases
Vinyl chloride	Used to make polyvinyl chloride, Which is in turn used to make many Plastic products Production of automobile upholstery/parts and housewares	Acutely, causes CNS effects such as dizziness, drowsiness, and headaches Chronic exposure can damage GI system and result in liver cancer
Benzene	Rubber manufacturing Chemical and petroleum production Shoemakers printers Steel workers gas station employees	Acutely, can cause dizziness, unconsciousness, and death Chronic exposure can lead to leukemia
Carbon monoxide	Forklift operators Foundry workers Miners Garage attendants Mechanics firefighters	Headache Tachypnea Cyanosis Syncope Binds strongly to heme O_2-carrying sites, decreasing available O_2 for the body
Hydrogen sulfide	Sanitation workers Farmers Natural gas drilling and refining workers in confined spaces, especially low-lying, marshy areas with hot weather and little wind	Health effects on concentration (ppm) Symptoms can vary from the smell of rotten eggs, to conjunctivitis and respiratory tract irritation, to immediate collapse with 1–2 breaths at levels of 700–1000 ppm
Pesticides	Agricultural workers Greenhouse workers Pesticide handlers (i.e., crop dusters, chemical manufacturers)	Wide variety of health effects, depending on type of pesticide involved Must consider pesticide toxicity, exposure, and absorption together when evaluating cases Workers covered by the agricultural worker Protection standard
Lead	Inhalation of lead fumes during burning and sintering Lead reclamation (i.e., battery recycling) Glassmakers, pottery workers military and law enforcement Munition workers welders	Lassitude Malnutrition Gingival lead line Encephalopathy Paralysis of wrist and ankles Renal failure
Cadmium	Smelting/refining Manufacturing/construction Plating processes Battery production Dietary intake: Shellfish, meat by products, liver, food stored in cadmium-glazed containers	Renal failure Chemical pneumonitis Lung cancer Osteomalacia Japanese rice paddies irrigated with cadmium-contaminated water resulted in an epidemic of osteoporosis in the 1940s Tobacco leaves concentrate cadmium, leading to chronic exposure in smokers

References [40, 43]

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employees and a work site walk-through. Following the initial investigation, management options can include improvement of ventilation rates, temporary removal from work environments, measures of environmental parameters by an industrial hygienist, cleaning of ventilation systems, and reengineering.

Mold

Of all the naturally occurring environmental contaminants, none seems to invoke as much fear as mold. Mold spores are omnipresent in the environment and reproduce in the presence of moisture. The most common types include Penicillium, Aspergillus, Cladosporium, and Alternaria. Molds can cause specific conditions including allergic asthma, but there is little evidence to support fears that airborne mycotoxins produce specific illnesses [47]. Similar to building-related illnesses, the evaluation of potential mold-related health conditions begins with an interview of the worker and an evaluation of the work environment that focuses on abnormal indoor moisture.

Remediation of mold and dampness in buildings may improve symptoms and consists primarily of removing the source of moisture and visible mold contamination [48]. Such cleaning could require intermittent, temporary relocation of employees. In all circumstances, clear communication with patients and the workforce is of paramount importance.

Specific Types of Occupational Examinations

As a branch of preventive medicine, one of the goals of occupational medicine is the prevention of injury and illness in the workplace. To fulfill this objective, the family physician may be asked to perform a variety of preventative and regulatory examinations for workers.

Post-hire, Preplacement Examinations

ADA prevents employers from discriminating against applicants based on disabilities. However, this protection from discrimination must be balanced with ensuring optimum safety of employees and the public. Typically performed at the request of an employer, the purpose of the post-hire, preplacement examination is to ensure that an employee can perform the essential functions of a job safely.

To ensure proper screening, it is important that the family physician have an adequate description of the employee's job duties and requirements. While this information could be obtained from the employee, a more reliable source would be a full job analysis document provided by the employer. Job analyses describe the duties and physical requirements of a work position.

Fit for Duty, Return to Work Examinations

Fit for duty (FFD) examinations are sometimes necessary when an employee has been off work for an extended period of time. Like preplacement examinations, the purpose of the FFD examination is to ensure an employee can still perform the essential functions of their job. An example where such an examination would be necessary is in the case of an employee who recently underwent a knee replacement and is hoping to return to work as a carpet layer.

Again, it is important that the family physician acquire adequate information to assess the employee's current medical status and work requirements when performing such assessments. In particular, the family physician must ensure that the patient does not pose a safety risk due to changes in medications.

Some family physicians are uncomfortable in providing fitness for duty assessments, especially when the outcome may be at odds with the wishes of the patient. In difficult scenarios, rather than putting the patient, other workers, or the public, at risk we suggest that family physicians might seek assistance of their occupational medicine colleagues.

Commercial Driver Examinations

Commercial driver 5250 fatal occupational injuries [6]. Forty percent of these fatalities were transportation-related events. Of the 2080 transportation-

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related fatalities, 3 out of 5 involved motorized land vehicles. With the high stakes involved, ensuring the safety of commercial drivers and public roads is one of the most important concerns of occupational medicine. Additionally, evaluation of commercial drivers is one of the most common avenues by which family physicians deliver occupational health care.

To obtain a commercial driver (CD) license, the driver must successfully meet the medical and physical requirements described by 29 CFR Part 391.41. This federal regulation provides in-depth information on medical requirements, such as blood pressure limits, and disqualifying medical conditions, such as epilepsy. Until recently, commercial driver medical certification examinations could be performed by a variety of medical providers. Unfortunately, due to a lack of standardized training for examiners, there was varying adherence to federal regulations and guidelines. To remedy this, the Federal Motor Carrier Association has required that after May 2014 that all commercial driver examinations be performed by certified commercial driver examiners [49]. Certified commercial driver medical examiners receive standardized training and must pass a certification examination. This move has reduced the number of available examiners and potentially provides family physicians with an important and lucrative occupational health opportunity.

Basic Med FAA Examinations

Another area of occupational medicine concern is aviation safety. For decades, Aviation Medical Examiners have monitored and assessed pilots for the Federal Aviation Administration. Traditionally, in-depth training was required before a physician could become an Aviation Medical Examiner. However, in 2016, the FAA launched the Basic Med program. This program allows some pilots the ability to be cleared for flying by any state licensed physician.

In order to qualify for Basic Med, a pilot must have held a medical certificate after July 14, 2006, must have a driver's license, must be examined by a state-licensed physician using the official Comprehensive Medical Examination Checklist, and complete online education.

While seemingly straightforward for healthy individuals, there are many important nuances and limitations that must be considered when performing the Basic Med examination. For example, pilots with a Basic Med certificate are limited to flying an aircraft with 6 occupants or fewer and a maximum certified takeoff weight of less than 6000 pounds, under 18,000 feet mean sea level, and at less than 250 knots. In addition, there are many medical conditions, such as depression, that require a special medical certificate from the FAA, called a Special Issuance, before a pilot may use Basic Med. The interested family physician is encouraged to review materials on the FAA website for further information on this path into aerospace medicine [50].

Comprehensive Occupational Health Programs

Many corporations and public sector organizations offer multifaceted programs designed to protect and improve the health of their employees. These programs include components such as health promotion, disability management, international health and travel medicine, benefit design, and workforce data analysis. These programs offer fascinating opportunities to improve health and medical outcomes for defined populations. With additional training, the family physician can assist with such programs.

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Problems Related to Physical Agents 49

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Heat

Definitions

Heat-related injury involves a spectrum of syndromes seen in individuals exposed to environmental heat. These injuries range from mild to life-threatening, and they include heat edema, cramps, heat exhaustion, and both non-exertional and exertional heat stroke. Heat stroke is a medical emergency characterized by a core body temperature >40 °C and altered mental status. Signs of organ failure may be present [1, 4].

Epidemiology

Nonathletic heat injuries and associated complications occur more often in the elderly due to impaired physiologic ability to respond to environmental heat. Athletes, military recruits, and outdoor laborers represent high-risk groups for exertional heat injury. The number of sports-related cases of exertional heat stroke (EHS), which is the most serious form of exertional heat-related injury (EHRI), has been increasing in the United States. In fact, between 1990 and 2010, heat illness was the third most common cause of sports-related fatalities in US high school and college football players [2].

Additional risk factors for heat injury include poor heat acclimatization, improper clothing/equipment, underlying cardiovascular, neurologic or psychiatric disease, diabetes, obesity, social isolation, use of alcohol and recreational drugs, and certain prescription medications such as those with anti-cholinergic or sedative effects [1].

Diagnosis

Clinical findings include elevated core body temperature as well as tachycardia, hypotension, flushing, and confusion. Since the elderly have impaired physiologic ability to respond to heat, their clinical presentation may be less obvious. Consequently, those above age 60 are particularly susceptible to heat injury and death [3].

Treatment

The management of mild and moderate heat injury involves moving to a cooler area, rest, and hydration. Medical attention is rarely required [1]. However, heat stroke is a medical emergency and requires establishing and supporting airway, breathing, and circulation (ABC's), rapid cooling (within 30 min), and management of complications. The initial target temperature should be 38.5 °C to 38.0 °C [4]. Various methods exist for rapid cooling. The most commonly used for non-exertional heat stroke involves spraying the patient with water while fans are directed toward the patient to stimulate evaporation and convection [5]. Submersion in cold or ice water is preferred for exertional heat stroke [4, 5]. Unless malignant hyperthermia is suspected, pharmacologic agents such as dantrolene, acetaminophen, and aspirin are not generally recommended as they are not effective and may exacerbate or potentiate complications such as hepatic injury [4]. The family physician should be cognizant of potential complications including cardiopulmonary dysfunction, neurologic injury, acute kidney injury, rhabdomyolysis, hepatic injury, and disseminated intravascular coagulation.

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Patient Education

Exertional heat injuries can be prevented through gradual acclimatization to the heat, physical conditioning, maintaining hydration, proper sideline preparation, and improving awareness and education of staff [2]. The National Athletic Trainers Association publishes guidelines for a heat acclimatization process [6]. Hallmarks include awareness, acclimatization, wearing loose-fitting clothing, mandatory breaks, and avoiding activities in extreme temperatures [1, 6].

Cold

Hypothermia

Background

Between 2006 and 2010, there were 10,649 deaths attributed to weather-related injury, with cold exposure and hypothermia approximating 63% of these deaths [7]. The cold-related death rate was lowest for children aged 5–14 but increased thereafter with increasing age, with the highest death rate among persons aged older than 75 [7]. Medical conditions such as heart disease, malnutrition, diabetes, and dementia can predispose individuals to cold injuries. Besides age and medical conditions, other risk factors include homelessness, intoxication, being an adventure traveler, and being a military recruit [8].

Definition

Hypothermia is defined as a core temperature to <35 °C. Mild hypothermia ranges from 35 °C to 32 °C, moderate from 32 °C to 28 °C, and severe at <28 °C. As the core temperature drops, compensatory shivering and consciousness decrease, while the risk of arrhythmia increases [9]. Measuring the core temperature may not always be feasible. In these cases, the "Swiss" hypothermia classification system, which incorporates clinical signs such as vital signs, level of consciousness, and presence or absence of shivering, is used to determine the probable core temperature [9]. The Swiss classification system has four stages, which are as follows: stage I – conscious and shivering; stage II – altered mental status and not shivering; stage III – unconscious, not shivering, vital signs present; and stage IV – unconscious, no vital signs detectable.

Treatment

A conscious, shivering patient likely does not need additional medical management besides seeking shelter; however, close observation is needed to ensure clinical deterioration does not occur. The initial management can be accomplished by passive rewarming. This includes carefully transferring the patient to a warm environment, removing wet clothing, and applying insulating clothing [8]. Active external rewarming involves application of heat packs, blankets, and hot water bottles ideally to the axilla, chest, and back, which can be used for both shivering and non-shivering patients. A warm shower or bath and active exercise should not be used for initial rewarming due to increased risk for an "afterdrop effect" (movement of cold blood from the peripheries to the central circulation) triggered by increasing peripheral blood flow [9].

If at stage II or a greater degree of hypothermia is suspected, infusion of warm IV fluids (38–42 °C) in addition to passive and active external rewarming is warranted if available. Efforts should be made for evacuation, and advanced cardiac life support may also be warranted. Individuals with profound hypothermia (<28 °C) or cardiac arrest should be transported to centers with extracorporeal life support (ECLS) capability. During transport, patients should remain horizontal to decrease risk of precipitating afterdrop and arrhythmias. Those with significant trauma should be transported to dedicated trauma centers [9]. A general rule is that hypothermic patients should be warmed to a core temperature of 37 °C prior to pronouncing death. However, patients with a lethal injury, significant airway obstruction, snow burial for more than 35 min, or serum potassium level greater than 12.0 mEq/L (12.0 mmol/L) can often be pronounced dead without an initial period of rewarming [8].

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Patient Education

Cold weather injuries are largely preventable with proper planning, protective equipment, and avoidance of prolonged exposure. Protective clothing and equipment include layering with a base layer made of moisture-wicking material such as polyester, middle layer with wool or fleece, and an outer layer made of a wind and moisture resistant material. Clothing and shoes should be loose to promote circulation [8].

Nonfreezing Cold Injury (NFCI) and Frostbite

Background

Nonfreezing cold injuries (NFCI) and frostbite are increasingly common. As with hypothermia, risk factors include age, skiers, and other practitioners of cold-weather activities, alcohol intoxication, homelessness, and inadequate clothing/protection [10, 12].

Definitions

NFCI occurs when tissues are exposed to a prolonged cold, wet environment at temperatures above freezing. Most cases occur in the feet and lower legs although upper extremities can also be affected. Frostnip and pernio are self-limited NFCI that do not commonly cause tissue damage or long-term sequelae. Immersion foot (trench foot) is a NFCI that occurs after prolonged exposure to wet, above-freezing conditions [8]. It is characterized by damage to the sympathetic nerves and vasculature of the feet that can also cause long-term sequelae such as sensorimotor and autonomic deficits [8]. Although classically described during World War I, immersion foot still occurs, particularly among the homeless [11]. A white vasoconstricted phase gives way to blue, mottled, edematous, and painful phase [8]. Some individuals are unable to continue to work outside in cold temperatures, which can affect their occupational as well as recreational opportunities. Prevention remains the key, with encouragement to use proper footwear, change into dry socks and/or gloves, as well as air drying feet several times a day.

Frostbite is a severe freezing injury that results in tissue destruction. The pathophysiology of frostbite consists of four phases: the prefreeze phase, freeze-thaw phase, vascular stasis phase, and late ischemic phase. In the prefreeze phase, the tissue cools, vasoconstriction occurs, but no ice crystals form. During the freeze-thaw phase, ice crystals form, causing cellular damage and derangement. Freezing is followed by thawing, which may cause inflammation and reperfusion injury, leading to further cell and tissue damage. Vascular stasis is marked by both dilation and constriction of blood vessels with concomitant blood leakage and coagulation. Finally, with late ischemia, further inflammation, microcirculation destruction, and cell death occur [10].

Although frostbite classically has four stages based on extent of physical damage, the extent of tissue damage after injury is often difficult to predict based on initial presentation or exam. Favorable signs include intact sensation, no cyanosis, and lack of blisters [12, 13]. Therefore, a simple two-tier system using either superficial (no or minimal anticipated tissue loss) versus deep (anticipated tissue loss) after spontaneous or formal rewarming is advocated by the Wilderness Medical Society [8, 10]. Triple-phase bone scanning with technetium pyrophosphate or magnetic resonance angiography (MRA) may allow an early diagnosis of viability and assist the physician and patient with probable level of amputation [8, 10, 13].

Approach to the Patient

Prehospital care of frostbite begins in the field and involves treating/preventing any hypothermia by seeking shelter, removing any wet clothing, drinking warm fluids, and placing the affected areas in a dry, warm area, such as a companion's axilla. Jewelry and other constrictive materials should be removed. Do not rub or put snow on the extremity. Ibuprofen (10–12 mg/kg divided twice daily) may help through antiplatelet and anti-prostaglandin effects. Tissue that thaws and then refreezes leads to further inflammation and damage. Therefore, the decision to rewarm must also include an evacuation plan. The patient should

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not walk on rewarmed feet unless only distal toes are affected [10].

The initial hospital management consists of correction of hypothermia, rapid rewarming in a 37–40 °C whirlpool, tetanus prophylaxis, and ibuprofen. Empiric systemic antibiotics are not indicated. Vasodilators (iloprost, pentoxifylline, and buflomedil) and tPA have been used with some success. Heparin, hyperbaric oxygen, and sympathectomy have been used as well in certain cases but not routinely recommended due to insufficient data [13].

Frostbite is largely preventable by maintaining core body temperature and hydration, mitigating medical conditions, utilizing medications that decrease perfusion, counseling regarding risks of alcohol consumption, proper clothing and equipment, and providing supplemental oxygen for hypoxic conditions as seen in high-altitude mountain climbers [10].

Radiation

Classification

Radiation involves the transfer of energy via high-speed particles or electromagnetic waves, and it can be ionizing or non-ionizing. Examples of ionizing radiation include X-rays and gamma rays along with alpha particles, beta particles, protons, and neutrons, the so-called particulate ionizing radiation. Examples of non-ionizing radiation include radio waves, microwaves, and the visible portion of the electromagnetic spectrum [14]. Whereas ionizing radiation has enough energy to displace electrons from orbits at multiple levels, produce free radicals, and penetrate human tissue, non-ionizing radiation cannot. Medical imaging and procedures using ionizing radiation now account for over one half of radiation exposure in the United States and some 98% of all artificial sources [15, 16].

The International System of Units (SI) of measurement for radiation dose is the gray (Gy), and for the biological risk of exposure, it is the Sievert (Sv). The effects of radiation on the body depend on the type of radiation, dose, amount of time exposed, route of exposure, and the types of tissues exposed [16]. Effects can range from no clinical significance to acute radiation exposure and increased risk of future cancers [14].

History

People are regularly exposed to radiation from cosmic radiation and radioactive elements in the environment; this is called background radiation and is largely unavoidable. The doses from background radiation are too low to cause radiation injury, although depending on geographic location, may contribute to small increases in cancer incidence [14]. Medical imaging is a significant source of man-made radiation with most of this radiation coming from computed tomography (CT) scans. As the availability of CT expands, the amount of radiation exposure is likely to increase around the world. To illustrate, a CT scan of the chest exposes a patient to about 7–8 millisieverts (mSv). A PA-lateral chest X-ray in comparison gives 0.1 mSv of radiation exposure. The background annual radiation exposure in the United States is estimated at about 3 mSv, and an exposure to an individual dose of greater than 50 mSv or a lifetime dose of greater than 100 mSv is considered above the threshold of safety [17]. Moreover, whereas exposure for healthcare and nuclear industry workers can be regulated, the exposure for patients cannot [18].

Children are especially vulnerable owing to their smaller size and increased organ sensitivity [15, 16]. There is evidence from atomic bomb survivors as well as radiation workers and recipients of radiation therapy that a dose-dependent relationship exists with ionizing radiation and an increased risk of cancer. One study found that in those less than 19 years old, more than 3 CT scans was associated with an increased risk of cancer [15, 19, 20]. The cancers most correlated to radiation exposure are leukemia, breast, lung, and thyroid [19]. Additionally, prenatal exposure to ionizing radiation has been associated with brain damage and other fetal anomalies [14, 16].

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Patient Education and Counseling

The most effective way to reduce the cancer risk from CT is to order fewer studies. It is estimated that approximately one third of all CT scans are not medically necessary. For example, the American College of Radiology in conjunction with the Choosing Wisely initiative recommends no imaging for an uncomplicated headache, no imaging for a suspected pulmonary embolism without a high pretest probability, and considering ultrasound before CT for children suspected of having appendicitis [21].

Radon is a radioactive, colorless, odorless gas produced from the natural radioactive decay of uranium. It is naturally released from the ground and is the main source of natural radiation [14, 16]. Exposure to radon gas has been associated with both lung cancer and non-cancer-related mortality [22]. In fact, radon is the second leading cause of lung cancer overall and the number one cause among nonsmokers [23]. Moreover, there is a synergistic risk of lung cancer among smokers also exposed to radon. In children, radon exposure has also been associated with asthma and upper respiratory infections. Many public health authorities including the Environmental Protection Agency recommend screening homes with low-cost and readily available screening kits [23].

Ultraviolet Light

Background

Ultraviolet light lies between the visible spectrum and X-rays on the electromagnetic spectrum. There is ample evidence that ultraviolet radiation in excess amounts can lead to skin and eye disease. There is also some evidence that it can affect the immune system [24]. There are three types of ultraviolet light classified based on wavelength: long or UVA, medium or UVB, and short or UVC [25]. All UVC is absorbed by the ozone, water, and gases above the earth's surface. Therefore, the ultraviolet light that reaches the earth's surface and contributes to human disease is largely UVA and UVB [24].

History and Physical Examination

Skin manifestations of excess ultraviolet exposure range from sunburn to malignant melanoma. UV radiation (UVR) also accelerates the aging of skin, leading to loss of elasticity and more coarse skin [24]. Ultraviolet exposure can play a pathogenic role in both non-melanoma and melanoma skin cancers. An estimated 63% of all cutaneous melanomas in Australia in 2010 were attributable to high ambient ultraviolet radiation [26]. Among high school students, tanning beds are a major source of ultraviolet exposure, especially among non-Hispanic white females. Fortunately, the overall prevalence appears to be decreasing [27]. With rising temperatures and ozone depletion, the incidence of skin cancers is projected to continue rising [25].

Ocular disease attributable to excess UVR includes eye and eyelid cancers, photokeratitis, pterygium, and cataracts. Cataracts are the most common cause of blindness globally and leads to significant morbidity. It is estimated that excess sunlight exposure is responsible for up to 20% of cataract burden around the world.

Patient Education

Although rigorous clinical trials proving the effectiveness of sun protection measures such as broad-brimmed hats, protective clothing, sunscreens, and sunglasses are lacking, common sense would suggest liberal use of these measures to protect against excess UVR [24, 26].

Electrical Injury

Background

In the United States, approximately 10,000 patients present to the emergency department with electrical burns or electric shock. In 2015,

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there were 565 recorded fatalities, and 25–50 people die each year from lightning strikes. Most electrical injuries are due to household or occupational exposures. Young children are often affected by household current, while adolescent males are affected by their high-risk behavior such as playing near high-voltage current sources, and adult males are affected by occupational hazards [28].

Approach to the Patient

Every organ system can be affected by electrical injuries resulting in thermal, electrophysiological, traumatic, and metabolic derangements. In addition, recognition of electrical injuries is challenging because they can resemble typical cardiac, trauma, and burn victims [28]. Electrical injury can cause burns, uncontrolled muscle contractions, arrhythmias, confusion, seizures, abnormal vision, weakness, and even paralysis, the onset of which can be delayed [29].

The initial management includes turning off the power source immediately and providing basic life support if needed. At the medical facility, the patient will be evaluated for burns, tissue damage, abnormal heart rhythms, and any other traumatic injuries. The family physician should note that although a skin burn may be seen at contact sites, most serious injuries are often not visible [29].

Noise

Background

At least 12% of the of the global population is at risk for hearing loss, which equates to over 600 million people. The most common preventable cause of hearing loss is exposure to excessive noise. Chronic noise exposure results in cochlear trauma which leads to hearing loss and tinnitus. Other symptoms associated with noise-induced hearing loss (NIHL) include reduced speech perception, vestibular dysfunction, stress, sleeping difficulties, and reduced performance [30]. Among noise-exposed workers, 23% have hearing loss, 15% have tinnitus, and 9% have both [31]. The highest risk occupations for hearing loss include mining, wood product manufacturing, construction, factory work, agriculture, utilities, transportation, and the military.

Recreational noise-induced hearing loss includes listening to personal devices, noisy entertainment, use of firearms, and attending clubs, bars, or concerts. In 2015, the World Health Organization (WHO) estimated that 1.1 billion young people worldwide could be at risk for developing hearing loss due to unsafe listening practices [30].

Counseling

Risk factors for developing noise-induced hearing loss includes genetics, deficiencies in magnesium or vitamin B12, pre-existing sensorineural hearing loss, use of certain medications, exposure to solvents, age, and chronic health conditions such as diabetes and hypertension [30]. Research is currently underway to determine the best hearing protective devices and treatment measures. In the meantime, education about noise-induced hearing loss to society and individual workers is important preventative steps.

Carbon Monoxide

Background

Carbon monoxide (CO) poisoning affects 50,000 people annually in the United States, with 15,000 of those being intentional poisoning. In 2014, there were 1,319 CO poisoning deaths, which is down from estimates of 2,700 in the mid-2000s. CO is a colorless, tasteless, odorless gas. It is formed by incomplete combustion of carbon compounds such as fire, engine exhaust, and faulty furnaces. In the blood, CO binds to hemoglobin (Hb) with high affinity and forms carboxyhemoglobin (COHb). CO competes with oxygen for Hb bonds and, by displacing oxygen, reduces the oxygen carrying capacity of hemoglobin. In

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addition, CO inhibits mitochondrial respiration which generates superoxide and leads to further damage of cells and tissues [32].

Diagnosis

CO poisoning is ideally diagnosed by a clinical triad of classic symptoms, history of exposure, and elevated COHb levels. Symptoms of CO poisoning include headache, dizziness, nausea, vomiting, dyspnea, fatigue, altered mental status, and chest pain [33].

In patients with suspected CO poisoning, the CO is traditionally measured by a co-oximeter analysis of venous or arterial blood for COHb levels. The nontoxic levels of COHb vary in the general population. Nonsmokers typically have a COHb level of less than 3%, whereas tobacco smokers have levels up to 10% [33]. Since conventional pulse oximetry cannot distinguish between COHb and oxyHb, it can miss significant COHb levels and profound hypoxia [32].

Treatment

The standard of care for treatment of CO poisoning is 100% normobaric oxygen (NBO) [34]. However, patients who receive hyperbaric oxygen therapy (HBOT) have a lower mortality rate than those who did not. In comparison with NBO therapy, HBOT leads to faster dissociation of CO from COHb. HBOT reduces the half-life of CO to 23 min compared to 80 min when administering oxygen through a nonrebreather mask [35]. In pregnant patients, there is a stronger indication for HBOT due to the slow dissociation of CO from hemoglobin in the fetus [34].

There are 5000 cases of pediatric CO poisoning annually, and children are more vulnerable because of their increased metabolic demand and inability to vocalize symptoms. They manifest different symptoms than adults and may present with symptoms resembling a viral illness with headache, nausea, and emesis being most common. NBO remains the mainstay of treatment with HBOT being controversial. However, limited research suggests that it is safe in children [36].

Counseling

Survivors of acute CO poisoning suffer long-term morbidity and some exhibit a near doubling of long-term mortality [32]. These individuals may have neurologic sequelae such as memory loss, difficulty concentrating, impaired language, and changes in affect such as depression or parkinsonism [33]. Their quality of life can be severely affected, and follow-up within 1–2 months is recommended to assess for psychiatric and neurocognitive deficits [32].

CO poisoning can be prevented by correctly installing furnace venting and running internal combustion engines in well-ventilated areas. Home CO alarms are also available, and automobiles with catalytic converters have reduced CO emissions [32]. Current research in pharmacology is focused on enhancing the CO dissociation from Hb with antidotes such as CO-scavenging molecules [32].

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Part XI

Injury and Poisoning

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Bites and Stings

50

Brian Jobe and Laeth S. Nasir

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Bites and stings account for a small but significant number of patients seen in the primary care setting. Family physicians can provide the patient, family, and community with anticipatory guidance regarding common hazards and appropriate care if a bite or sting does occur.

Mammalian Bites

Most mammalian bites are from dogs or cats. Children are the most frequent victims of dog bites [1]. Most of the dogs involved are known to the victim and were considered friendly prior to the biting episode. Injuries inflicted by cats tend to involve the hand and upper limb.

Clinical Presentation

Significant dog bites tend to be lacerations, often with crushing or tearing of tissue. Bites are most often sustained on the extremities, head, and neck. In children, dog bites may penetrate the skull. Because of their needle-like teeth, cat and rodent bites are usually puncture wounds, often involving tendons or joint spaces. A multitude of organisms reside in the mouths of all higher primates. For this reason, these bites are notoriously predisposed to infection. Human bite wounds most commonly result from conflict or contact sports. Potentially, the most serious human bite wound is the "clenched-fist" injury. This injury is sustained when the victim strikes an adversary in the mouth with a clenched fist and suffers a laceration inflicted by the other's teeth. Microorganisms may be inoculated into the deep tissues of the hand, resulting in a devastating infection.

Diagnosis

All bites are examined meticulously for foreign bodies and devitalized tissue. Radiographs are considered if there is the possibility of fracture or a retained foreign body. The medical record should include information regarding the site, depth, and circumstances of the biting episode, as well as a sketch of the injury.

A clenched-fist injury should be examined after reproducing the position of the hand when the injury occurred. Otherwise, penetration of the wound into the deep tissues of the hand may not be appreciated.

Management

All mammalian bites should undergo copious irrigation with sterile saline. A 19-gauge or larger needle on a syringe is often used to generate a high-pressure stream. Careful debridement of all devitalized tissue is necessary (see Patient-Centered Medical Home. Further management depends on classifying the wound as high risk or low risk for infection. There is general agreement that high-risk bites are those involving the hands or feet, injuries older than 6–12 h, deep

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puncture wounds, crush injuries, human bites, cat bites, and bites sustained by elderly or immunocompromised individuals. Bites involving deep structures such as bones, joints, or tendons are also at high risk of infection. Individuals with high-risk bites should have their wounds debrided, packed, and reevaluated in 72 h to consider delayed primary closure. Prophylactic antibiotics should be administered. In practice, many bites otherwise considered high risk are primarily repaired if functional or cosmetic considerations strongly warrant it. Deep puncture wounds, bites of the hand, and wounds that present late should never be closed primarily [2]. Bite wounds involving the deep tissues of the hand should be surgically debrided, packed, immobilized in the position of function, and elevated. These injuries require intravenous antibiotic therapy. Low-risk wounds may be sutured immediately; antibiotic prophylaxis is not required. Cultures of an uninfected wound are not useful.

Human bites may transmit hepatitis B and C as well as herpes simplex virus. Prophylaxis against hepatitis B may be achieved by administering hepatitis B immune globulin (HBIG) 0.06 mL/kg and hepatitis B vaccine. The potential for human immunodeficiency virus (HIV) transmission by human bites is thought to be low, although there are case reports of transmission by this route [3–5]. The need for tetanus and rabies vaccination should be assessed.

Prophylactic Antibiotics

Patients with high-risk wounds should receive a 3–5-day course of prophylactic antibiotics. Amoxicillin-clavulanate 875/125 mg bid is an appealing agent for prophylaxis of human and animal bite wounds. Its spectrum of activity includes *Pasteurella multocida*, *Staphylococcus aureus*, streptococci, *Eikenella corrodens*, and β-lactamase-producing oral anaerobes. Penicillin-allergic patients may receive cefuroxime 500 mg bid or doxycycline 100 mg bid.

Established Infections

For established infections, empiric treatment with ampicillin-sulbactam 1.5–3.0 g IV q6h, cefoxitin 1 g IV every 6–8 h, or ertapenem 1 g IV every 24 h is recommended [6].

For patients with a definite penicillin allergy, alternatives include clindamycin 600 mg IV every 6 h plus a fluoroquinolone such as ciprofloxacin 400 mg IV every 12 h.

Rabies Prophylaxis

Rabies is a nearly uniformly fatal condition once symptoms begin to manifest. Therefore, a high index of suspicion for this infection must be maintained after any mammalian bite. Bats and other wild mammals are currently the major source of rabies in the United States. Assessment of risk involves a thorough history and physical examination. A break in the skin from the teeth or claws of an infected animal or contact with saliva on mucous membranes or broken skin constitutes exposure. The decision to apply prophylaxis is then guided by the specific situation and animal species. In general, bats, skunks, raccoons, woodchucks, foxes, and other wild carnivores should be regarded as rabid and immunoprophylaxis administered. If the animal is captured, it should be killed immediately, and the head sent under refrigeration to an appropriately equipped laboratory for fluorescent antibody examination. If the test is negative, the vaccination series may be discontinued. Domestic dogs, cats, and ferrets that are otherwise healthy should be confined and observed for a period of 10 days. If they remain asymptomatic, prophylaxis is unnecessary. The management of all other exposures, from either wild or domestic mammals, should be decided after consultation with the local health department.

Early, thorough wound cleansing is necessary to reduce the viral inoculum. Wounds are flushed with soap and water. Suturing the wound is avoided if possible. Human rabies immune globulin (HRIG) is administered in a dose of 20 U/kg

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body weight to both adults and children. This dose should not be exceeded, as passive antibody may interfere with response to the active vaccine. Half of the dose is infiltrated around the wound, if feasible, and the rest given intramuscularly in the gluteal area. Active immunization is accomplished by human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) the first dose given simultaneously with HRIg with repeat doses on days 3, 7, and 14, in immunocompetent patients and repeat doses on days 3, 7, 14, and 28 in immunocompromised patients. The active vaccine is administered intramuscularly in the deltoid. In infants it is given in the anterolateral thigh [7].

Prevention

The role of education in the prevention of these injuries cannot be overemphasized. Dog bites are reported to be among the top 12 causes of nonfatal injury in the United States [1]. Situations reported to be potentially dangerous include approaching dogs immediately after entering their territory, waking a dog from sleep, and teasing or playing with a dog until it becomes overexcited [8]. Male dogs and dogs that have not been neutered are more likely to bite [1, 9].

Family and Community Issues

Most dog bites are preventable. Parents should be counseled never to leave a child alone with a dog, and children should be taught never to approach an unfamiliar dog. They should also be warned of the danger of startling animals. Children should learn to recognize signs of distress in familiar animals and be warned not to disturb them when they are exhibiting this behavior.

Spider Bites

In North America, two species of spider account for most medical problems after bites. The brown recluse spider (*Loxosceles reclusa)* is found primarily in the south central regions of the United States but may be transported anywhere. It is a small (1–2 cm) tan to dark brown spider with a violin-shaped pattern on the back. It produces a venom containing sphingomyelinase D, which causes endothelial swelling, platelet aggregation, and thrombosis. The black widow spider (*Latrodectus mactans*) has a shiny black color with a red hourglass-shaped marking on the ventral abdomen. Black widow venom contains α-latrotoxin, a potent neurotoxin.

Clinical Presentation

Brown recluse spider bites are painless or only mildly painful. Within 2–8 h, though, severe local pain may occur. An erythematous or cyanotic macule ("volcano lesion") may appear at the site of the bite often followed by a deep necrotic ulcer, which may take months to heal. Systemic absorption of toxin may lead to fever, malaise, vomiting, skin rash, and jaundice. Hemolysis and disseminated intravascular coagulation (DIC) may occur. Desquamation of the extremities, petechiae, and skin rashes may appear as late as 3 weeks after the bite [10].

Black widow spider bites are often painless, but 20 min to several hours later, localized pain, cramps, and fasciculations may occur. Progression to pain and rigidity in the abdomen, shoulders, and back often follows. Autonomic signs such as nausea, vomiting, fever, dizziness, hypertension, and sialorrhea may occur.

Diagnosis

Often the diagnosis of a spider bite is made presumptively by the victim. One study found that 90% of suspected spider bites were actually bites from other insects or manifestations of disease states [11]. For this reason, it has been suggested that in the absence of conclusive evidence as to the identity of the culprit, such bites be labeled "arthropod bite, vector unknown" in the medical record [12].

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Management

For most spider bites, wound care, ensuring current tetanus immunization status, and monitoring for infection are the only interventions required. Local symptoms are controlled through the use of ice, analgesics, and antihistamines.

Severe systemic symptoms due to brown recluse spider bites may require treatment with enteral or parenteral corticosteroids. Based on studies on rabbits, brown recluse envenomations that only have local effects do not respond to treatment with steroids, antihistamines, or hyperbaric oxygen therapy [13].

If available, specific antivenin (Antivenin, Merck, West Point, PA) may be the management option of choice for all significant envenomations due to black widow spiders [14–16] (Table 1). Parenteral narcotics, intravenous diazepam, or methocarbamol are useful for muscle cramps, as are prolonged hot baths.

Prevention

Clearing away debris, plugging openings into houses, wearing gloves and long pants, using insecticides, and avoiding heavily infested areas are the major preventive steps that can be taken to avoid bites.

Hymenoptera Stings

Stings by bees, wasps, hornets, and ants are common in most climates. Their shared manifestation is the production of localized dermal wheal and flare reactions. Full-blown anaphylaxis occurs in a subset of individuals. Domestic honeybees are relatively nonaggressive in defense of their colony. In contrast, Africanized bees ("killer bees"), endemic to parts of Arizona, Texas, and New Mexico, engage in massive stinging attacks that are often fatal. Fire ants are endemic to many southern states, and their bites are sustained by a large proportion of the population in infested areas each year.

Clinical Presentation

Wheal and flare dermal lesions are the most common presentation. The fire ant often makes a series of stings, leading to a characteristic semicircular pattern of sterile pustular lesions. Systemic toxicity may develop in the adult if more than approximately 50 bee stings are

Table 1 Antivenins

Antivenin	Indication	Dosage
Antivenin (Crotalidae immune fab) (ovine) (CroFab® BTG international) polyvalent	North American pit viper (crotalid) envenomation	4–6 vials IV q hour until symptom control Once controlled 2 vials q 6 hours x 3
Antivenin (ANAVIP® (Crotalidae immune $F(ab')_2$) (equine) (rare disease therapeutics, Inc.)	North American rattlesnake envenomation is the only FDA-approved indication	10 vials q hours until symptom control then 4 vials q hour as needed for re-emerging symptoms
North American coral Snake antivenin (equine) *(Micrurus fulvius)* (Wyeth pharmaceuticals, LLC a subsidiary of Pfizer, Inc.)	Coral snake envenomation-eastern coral snake and Texas coral snake	Initially 3–5 vials Persistent symptoms repeat 3–5 vials
Antivenin black widow spider antivenin (equine) *(Latrodectus mactans)* (Merck &co., Inc.)	Black widow spider envenomation	1–2 vials 1 M (IV in severe cases)
Scorpion antivenin Centruroides (scorpion) immune $F(ab')_2$ (equine) (ANASCORP® rare disease therapeutics, Inc.)	Bark scorpion envenomation	3 vials initially IV Pediatric and adult patients and thereafter guided by symptoms subsequent 1 vials after 60 min as needed

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sustained simultaneously. Generalized edema, dizziness, weakness, and vomiting may be followed by DIC, rhabdomyolysis, and acute tubular necrosis.

Management

The lesion is examined for the presence of a stinger. If one is present, it is promptly removed. Squeezing the venom sac is avoided.

Applying ice to the lesion reduces pain. Topical steroid preparations and oral antihistamines may be used for local reactions. Calamine lotion and cool, moist dressings are useful. Treatment of massive envenomation is identical to that for anaphylaxis, and it may be difficult to differentiate between the two conditions.

Prevention

Individuals at risk should avoid perfumes and brightly colored clothing while outdoors. People who clear vegetation and discarded junk are at increased risk of being stung. Individuals with a history of anaphylaxis after stings should be offered desensitizing immunotherapy. They should also carry an anaphylaxis self-treatment kit (Ana-Kit or EpiPen injectors).

Snakebite

There are two families of poisonous snakes in the United States. Elapidae, or coral snakes, are found in the South. Brightly colored with black, red, and yellow rings, they produce a neurotoxic venom. They rarely bite humans. Crotalidae, or pit vipers, which include rattlesnakes, cottonmouths, and copperheads, are distinguished by heat-sensing organs, or "pits," in the area between the eye and the nostril. Crotalid toxin primarily causes hemolysis, hemorrhage, and local soft tissue damage, although a few Mojave rattlesnakes produce a neurotoxic venom [10].

Clinical Presentation

Patients presenting after snakebite may display extreme anxiety, and it is important not to mistake it as evidence of envenomation. Local tissue changes include pain, edema, bullae, and ecchymosis. DIC and acute renal failure may occur. Coral snake envenomation may result in bulbar and respiratory paralysis.

Diagnosis

All patients who have sustained a venomous snakebite should undergo a complete evaluation regardless of the initial presentation, as effects can occur unpredictably for up to 12 h after the bite. In addition to the history and physical examination, a complete blood count, DIC screen, creatine phosphokinase assay, electrocardiogram, and urinalysis are recommended and may be repeated at intervals. Serial circumferential measurements of the affected extremity should be performed to monitor swelling. Consideration should be given to prophylactic endotracheal intubation in patients having sustained a bite of the face or head [10].

Management

Once an initial evaluation is done, contact should be made with the state poison control center to discuss the type of snake, location of bite, and signs and symptoms that the patient is having. Poison control can act as an important resource for discussion of administration of antivenin as well as other aspects of management. Intensive supportive care is often indicated. Antivenin is the only specific treatment available (Table 1). Its use for crotalid snakebites is recommended only if there is clinical evidence of envenomation [10]. Clinical assessment of the snakebite severity guides the amount of antivenin administered. Several objective scoring systems are in use [16, 17]. For minimal envenomations, up to 10 vials of antivenin are used and for moderate envenomation 10–20 vials [10]. The antivenin for crotalids

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(rattlesnake, copperheads, and water moccasin/cottonmouth) is Crotalidae polyvalent immune Fab (ovine) and is reconstituted in 10 mL of saline for each vial and diluted in 250 mL of saline to infuse. Start with 4–6 vials in and run the IV infusion over 60 min, proceeding slowly over the first 10 min at a 25–50-mL/h rate with careful observation for any allergic reaction. If no allergic reaction occurs, increase infusion rate to the full 250 mL/h until completion. Give an additional 4–6 vials followed by 2 vials every 6 h for 18 h for 14–18 vials total as indicated [18]. For severe cases, 20 or more vials of antivenin may be necessary. In children these doses may have to be increased by as much as 50%. A new antivenin (ANAVIP®) is available for rattlesnake bites only that is dosed based on symptoms also but has a longer half-life likely because it is a larger molecule. Effectively, it will continue to have benefit against the late effects of rattlesnake venom – in particular the coagulopathies. Specific antivenin should be administered to anyone sustaining a bite from a coral snake, regardless of initial presentation, as symptoms may progress rapidly once they appear. Antivenin administration is associated with anaphylaxis and serum sickness in a significant percentage of patients so it is important to gather history about sensitivity to horse proteins and to run a test dose for coral snake antivenin and the new rattlesnake specific antivenin of 1–2 mL over 3–5 min.

Prevention

Prevention is practiced by avoiding infested areas and high-risk behaviors, such as turning over logs and stones in the wild. Boots and long trousers provide significant protection from snakebite. Carrying a light while walking at night is an effective snake repellent.

Other Arthropods

Many other arthropods, including mosquitoes and ticks, target humans among their hosts. In the United States, mosquitoes transmit a number of arboviral encephalitides. Tick-borne diseases include Lyme disease, typhus, babesiosis, Rocky Mountain spotted fever, and ehrlichiosis (see ▶ Chap. 44, "Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome"). Scorpions native to the United States are not significantly toxic except for the bark scorpion (*Centruroides exilicauda)* endemic to Arizona and New Mexico.

Clinical Presentation

The most common presentation of a tick bite is the discovery of an attached tick. Ticks have a barbed feeding organ, or hypostome, through which they suck blood. This feeding mechanism is buried under the skin of the host, making removal of the tick difficult. Patients may also present with sequelae of a tick bite, such as erythema migrans. Rarely, injection of a neurotoxin by a female *Dermacentor andersoni* or *Dermacentor variabilis* tick results in a rapidly ascending motor paralysis known as "tick paralysis."

Most scorpion stings result in localized pain and swelling only. Systemic toxicity presents with localized numbness and paresthesias, followed by nausea, vomiting, dyspnea, and sialorrhea. Hypertension, involuntary motor activity, and seizures may occur. The severity of presentation for bark scorpion sting guides the use of the antivenin and should be done in consultation with the state poison control center. The antivenin is especially helpful for use in children – who are most commonly stung by scorpions and vulnerable older patients.

Diagnosis

Ticks may attach anywhere but are often found at the hairline or on the scalp. Tick bites may induce persistent granulomas or ulcers at the site of attachment. Tick paralysis often presents with flaccid paralysis. Bulbar paralysis and respiratory depression may occur. Cerebrospinal fluid examination is unremarkable.

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Management

An attached tick is removed by grasping it as close to the host's skin as possible with tweezers or protected fingers. Steady traction should be applied to detach the tick. Pulling too hard decapitates it and leaves the mouth parts embedded in the skin. Tick paralysis resolves spontaneously after removal of the tick.

Patients who display evidence of systemic toxicity from scorpion stings require supportive care. Beta-blockers are used for management of severe hypertension. Specific antivenin is available for severe envenomations. This is in the form of an antivenin developed from horse serum. The immunoglobulin is administered based on the severity of presentation of the patient. Contact the Poison Control Center for management decisions which will focus on degree of envenomation and the risk benefit of administration of the bark scorpion antivenin [19].

Prevention

Protective clothing should be worn when traveling in infested areas to avoid tick and mosquito bites. Individuals at risk should be counseled to carry out a visual inspection of the entire body twice daily to detect and remove any attached ticks. An insect repellent containing diethyltoluamide (DEET) should be applied to all exposed skin. Permethrin 0.5% spray (Nix, Elimite) applied to clothing provides further protection. There is hope for a Lyme disease vaccine in the near future. A previous vaccine, LYMErix, was withdrawn from the market voluntarily in 2002 [20].

Marine Animal Stings

In the United States, stingrays and coelenterates (sea anemones, jellyfish, corals) cause most of the significant human injuries or envenomations.

Clinical Presentation

Most commonly, the victim steps on a stingray hidden under the sand and is envenomated by a spine on the dorsum of the creature's tail. Stingray venom contains serotonin and proteolytic enzymes. The victim often experiences immediate pain and swelling of the affected extremity. Nausea, vomiting, weakness, diaphoresis, cramps, and dyspnea may occur.

Coelenterates (jellyfish) have thousands of stinging organs called nematocysts on their tentacles. Contact with these organs triggers the sting, which penetrates the skin and releases toxin.

Coral injuries are abrasions with a risk of secondary infection of the wound with organisms such as Staphylococcus aureus [21]. The exception is the fire coral which has stinging nematocysts similar to a jellyfish [22].

Diagnosis

Wounds inflicted by stingrays are often jagged and edematous. Pieces of the dorsal spine may be embedded in the wound or surrounding tissue.

Coelenterate stings present with a stinging or burning sensation involving the affected area. Erythema and papules appear in a linear distribution. Systemic symptoms include headache, nausea, muscle pain, spasm, and tachycardia. Massive envenomations have led to death.

Management

After soaking the stingray-induced wound in hot (45 °C) water for up to 90 min to deactivate the toxin, the wound is carefully irrigated and debrided. It is then packed and reevaluated at 72 h for delayed primary closure. Tetanus vaccination status is assessed and updated if necessary.

Soaking areas affected by coelenterate stings in hot, uncomfortable (not scalding) water for 5–10 min every 15 min up to 2 h helps deactivate toxins [12]. Any adherent tentacles are removed with gloved hands, and the affected areas may be

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shaved with a razor or sharp knife to remove any remaining nematocysts. A steroid-containing cream may be applied.

Prevention

Individuals should consider wearing sandals or shoes when wading in areas where stingrays or coelenterates are found. Stingrays, jellyfish, and other marine animals must be avoided, even when apparently lifeless.

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Poisoning

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Deepa Sharma and Nina Sharma

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The family physician is often a patient's first contact for health-related concerns and therefore knowledge of the proper initial evaluation and treatment of ingested poisons is crucial. This chapter should provide the office-based family physician with a sufficient overview in the diagnosis and management of common oral poisonings. The ingestion of acetaminophen, antidepressants, aspirin/salicylates, and opioids will be presented.

Introduction

Poisoning refers to contact with a substance that may result in toxicity. Toxicity may result from excess amounts of otherwise nontoxic substances, such as common medications. Poisonings are therefore dose related, distinguishing them from hypersensitivity reactions which are unpredictable. Symptoms of poisoning/toxicity may vary, and the following discussion will provide an overview of common syndromes of particular classes of drugs [2]. While poisoning may occur via various routes such as oral, inhalation, injection, and exposure of body surfaces, this chapter will focus on oral ingestion of specific common medications acetaminophen, antidepressants, aspirin/salicylates, opioids, and benzodiazepines.

Accidental poisoning is common among children, adolescents, adults, and the elderly. This chapter will focus on the office-based family physician's ability to recognize poisoning and its initial evaluation and management. The information presented today does not include intentional poisoning in individuals attempting suicide, or victims of attempted harm by others.

Signs and Symptoms

Signs and symptoms of poisoning may vary depending on the substance ingested and the individual affected. There are common toxic syndromes (Table 1) that suggest particular classes of substances; however, if multiple substances are ingested, the patients is unlikely to have symptoms characteristic of a single substance. Symptoms develop either immediately after contact, but may also be delayed. When delayed, the toxicity is a result of the metabolite and not the parent substance. Ingested toxins generally cause systemic symptoms [1].

Diagnosis

In the event that a patient contacts the family physician office by telephone or email, a rapid triage protocol should be in place. Appropriately trained health care team members should be able to quickly obtain and document any available history from the patient or representative which includes name, dose, amount of substance ingested, when ingested, intentional/

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Table 1 Common toxic syndromes

Drug	Symptoms and physical findings	Laboratory findings
Acetaminophen (Tylenol)	Nausea, vomiting, malaise, right upper quadrant abdominal pain, jaundice, confusion, somnolence; coma may develop later	After 24 h, increased AST (>1000 IU/L is characteristic), increased ALT, increased bilirubin, PT may increase
Salicylates	Nausea, vomiting, hyperpnea, tinnitus, fever, disorientation, lethargy, coma, seizures, diaphoresis, abdominal pain	Respiratory alkalosis with progressive anion-gap metabolic acidosis, hyperglycemia/hypoglycemia, hypernatremia/hyponatremia, hypokalemia
Cyclic antidepressants	CNS excitability, confusion, blurred vision, dry mouth, fever, mydriasis, seizures, coma, arrhythmias, hypotension, tachycardia, respiratory depression; physical condition can rapidly change	ECG findings of increased QRS interval >0.10 s, sinus tachycardia, conduction abnormalities
Benzodiazepines	Drowsiness, lethargy, dysarthria, ataxia, hypotension, hypothermia, coma, respiratory depression with severe overdoses	No characteristic findings
Narcotics	Drowsiness, nausea, vomiting, miosis, respiratory depression, cyanosis, coma, seizures, bradypnea, noncardiac pulmonary edema	With severe respiratory depression, hypoxemia, hypercarbia, respiratory acidosis, rhythm disturbances, pulmonary edema

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *PT* prothrombin time, *CNS* central nervous system, *ECG* electrocardiogram

unintentional, and clinical status. The health care team may refer the patient to emergency medical services (EMS) for immediate medical attention, emergency room evaluation, or utilize local poison control centers for additional guidance.

PoisonHelp.org is an interactive website that provides critical triage and information on how to manage exposures to potentially toxic products, poisons, and medications. Users are prompted to answer a few questions regarding a human exposure to any of 1114 generic substances that encompass now more than 449,000 unique products. Recommendations are vetted by specially trained physicians, pharmacists, and nurses from our nation's 55 poison control centers. The website can be accessed from any computer or mobile device and is free, confidential, and available 24/7 [2].

For the patient who presents to the office scheduled/unscheduled the first priority is initial evaluation of the overall status of the patient. In cases of severe poisoning, rapid intervention to treat airway compromise or cardiopulmonary collapse may be necessary requiring the activation of emergency medical services (EMS). Poisoning may or not be known at the time of presentation, it should be suspected in patients with unexplained symptoms and especially altered mental status. Careful attention for intentional/self poisonings in adults as multiple substances may be involved and can have unpredictable symptom course and clinical stability.

For all patients, history is the most valuable tool, although sometimes the most difficult to obtain. History should be taken from all available sources, including the patient, friends, family, relatives, and rescue personnel. Medical record and pharmacy record information may also be useful to obtain information related to access to substances. If unknown pills are discovered, poison control centers are an important and useful resource for identification, further evaluation, and management guidance [1].

A physical exam can be helpful to determine if the classic toxic syndromes suggest a particular class of drug, if there is evidence of breath odor suggestive of alcohol use or needle marks/tracks indicating injected drug use. Immediate attention should be directed to evaluation of the airway and ventilation, cardiac function/perfusion, level of consciousness, and mental status. Unstable patients should be connected to any available cardiac monitor, oxygen if available, and measurement and documentation of vital signs every 5 min until stabilized or transferred should be noted [1].

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Once the patient is stabilized a more detailed physical exam is necessary to evaluate the extent of poisoning and the presence of concurrent conditions which contribute to impact of toxicity. The physical findings may also help the clinician to determine if the toxin is a stimulant or depressant. Signs of toxic ingestion of stimulants include mydriasis (pupil dilation), tremor, tachycardia, irritability, mania, diaphoresis, and convulsions. When toxic amounts of depressants are ingested, signs include lethargy, decreased responsiveness, miosis (pupil constriction), hypothermia, and coma. Consulting a professional/experience colleague or regional poison control center can help with additional physical findings [1].

Point-of-Care Testing

For poisonings that have cardiovascular effects or of an unknown substance, in office cardiac monitoring and obtaining an EKG may be helpful. Point-of-care blood glucose testing may also be helpful for concerns of hypoglycemia.

Laboratory Evaluation

For the office-based family physician, laboratory evaluation of poisoning may be limited, unless the physician has an onsite laboratory with the capability of rapid results. The standard toxic screens both urine and serum are qualitative and may only check for a limited number of substances or their metabolites. Unless the result of the laboratory evaluation is rapidly available and will guide treatment, in the office setting there is limited use.

Decontamination

Gastric Emptying

Gastric emptying is no longer routinely performed. Previously, it was considered if it could be done within 1 h of a life-threatening ingestion. Since many poisonings manifest too late, and may not always be life threatening, it is not always clearly indicated. Furthermore, ingestion of a caustic substance is a contraindication to this procedure.

When gastric emptying was used, gastric lavage was the preferred method. Gastric lavage does have associated complications such as aspiration or rarely oropharyngeal or esophageal injury. Further discussion of this no longer routinely performed method will be deferred at this time [1].

Ipecac

Ipecac is an agent used to induce vomiting through irritation of the gastric mucosa and stimulation of the chemoreceptor trigger zone in the medulla. It is no longer manufactured in the USA because of concerns for safety and ability to improve outcomes for patients who have been poisoned [3].

Activated Charcoal

Charcoal is usually given, frequently when unknown or multiple substances have been ingested. The added risk in its use includes vomiting and aspiration, however it does reduce overall morbidity and mortality. If being used, it should be given as soon as possible.

Activated charcoal is an adsorbent that works by binding the toxin throughout the GI tract to reduce systemic absorption. It is given as a single oral dose between 25–100 g within 1–2 h of the toxin ingestion to maximize efficacy. Doses are often mixed with juices or carbonated beverages to improve their palatability [4].

Although activated charcoal binds most substances, Table 2 below outlines the agents for which the use of activated charcoal is NOT recommended:

Acetaminophen

Acetaminophen is consistently one of the most common toxic drug exposures. Ingestions of 4 g or greater may cause injury in select patients. In general, acute doses of 150 mg/kg or 10 g in adults

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Table 2 Agents to AVOID use of activated charcoal (AC)

	Rationale
Acids – *mineral acids, boric acid* **Alkalis** – *cleaning solutions, bleach, and dishwasher detergent*	Vomiting can be damaging and the AC may cause discoloration of the stomach lining and therefore interfere with endoscopy
Alcohols **Organic solvents** – *acetic acid, acetone, ethylene glycol, glycerin, and toluene* **Cyanide/Organophosphates** – *insecticides, herbicides, and antihelminthic drugs* **Metals** – *arsenic, iron, lead, lithium, and mercury*	Bind poorly, which necessitates large doses of AC that are difficult to ingest

Complications include aspiration, accidental administration into the lung, emesis, constipation, and gastric obstruction. Contraindications include unconscious state or otherwise unable to protect the airway without endotracheal intubation and recent GI surgery

and 200 mg/kg in children are considered toxic. It is recommended that doses exceeding this threshold be managed in a health care facility.

Pharmacokinetics

The mechanism of toxicity is caused by the active metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which can lead to oxidant cell injury, hepatic failure, and death. Around 90% of acetaminophen undergoes phase II conjugation to glucuronide and sulfate conjugates that are excreted in the urine. An additional 2% is excreted unchanged in the urine. The remaining amount (8–10%) is converted by cytochrome P450 (CYP2E1) to NAPQI. NAPQI is normally converted by glutathione to cysteine conjugates, which are renally excreted. In an overdose, the sulfation and glucuronidation pathways become saturated, leading to glutathione depletion and a subsequent buildup of NAPQI [5].

Clinical Presentation

Mild poisoning may not cause symptoms, and often acute poisoning symptoms are usually minor until >48 h after ingestion.

Four clinical phases are associated with an acetaminophen toxicity [6]:

Phase I – within the first 24 h after ingestion: Patients may present with minimal or no signs of distress. Potential signs and symptoms include nausea, vomiting, diaphoresis, and anorexia.

Phase II – within 24–48 h after exposure: Marked by initial damage to the hepatocytes. Patients may present with right upper quadrant pain, increases in liver transaminases, elevated total bilirubin concentrations, and prolonged prothrombin time.

Phase III – within 72–96 h after initial exposure: The peak of the hepatotoxic effects. Patients may present with lactic acidosis, acute renal failure, acute pancreatitis, and fulminant hepatic failure, as evidenced by jaundice, extensive coagulopathies, hypoglycemia, and hepatic encephalopathy.

Phase IV – about 1 week after exposure: Marks the recovery phase if the patient survives phase III.

Management

The goal of treatment is to prevent the development of hepatic toxicity and reduce mortality. Gastric decontamination with a single dose of activated charcoal can be considered if the patient presents within the first hour after exposure, is not vomiting, and has no alterations in mental status.

Antidote therapy is recommended with N-acetylcysteine. The mechanism of action for N-acetylcysteine is to increase the synthesis and bioavailability of glutathione, substitute for glutathione by binding to the reduced sulfur group of NAPQI, and supply a substrate for sulfation, thereby increasing the nontoxic metabolism.

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Guidelines suggest that acetylcysteine treatment should be administered to patients within the first 8 h of exposure if they can be stratified as being at possible or probable risk of hepatotoxicity by the Rumack-Matthew nomogram [7] (Fig. 1 in current textbook). If patients cannot be stratified either because of unknown time of ingestion or inability to perform acetaminophen serum assays, they should receive acetylcysteine if any of the following conditions apply (Table 3):

(a) Increased alanine aminotransferase (ALT) concentration
(b) Serum acetaminophen levels greater than 20 mcg/mL
(c) History of chronic ingestions exceeding 4 g/day with an elevated serum ALT concentration

Intravenous acetylcysteine is preferred because of its decreased overall administration time (21 h versus 72 h for oral) and minimal GI adverse effects. Oral acetylcysteine is dosed for 18 total doses; doses may be repeated if emesis occurs within 1 h of a dose. To improve palatability, doses may be diluted in juice or carbonated beverages in a covered cup with a straw. Antiemetics may be administered if significant nausea or vomiting occurs. Although treatment guidelines recommend 18 total doses of acetylcysteine administered over 72 h for oral acetylcysteine therapy and 20 h of the intravenous infusion of acetylcysteine, many poison control centers recommend early discontinuation (or prolonged therapy) if the following conditions are met [8]:

(a) Serum acetaminophen concentrations are undetectable or less than 10 mcg/mL
(b) ALT levels normal (60 IU/L or less) or improving. Some clinicians also advocate an INR (international normalized ratio) of 1.3 or less
(c) The patient is clinically improved

Patients should be monitored for improvement in vital signs and mental status. The following laboratory values should be monitored periodically for improvement as well as for potential worsening.

(a) ALT, aspartate aminotransferase (AST), total bilirubin, and prothrombin time
(b) BUN and SCr
(c) Serum electrolytes
(d) Fulminant hepatic failure: Serum bicarbonate, serum lactate, arterial blood gas, serum glucose, and ammonia levels

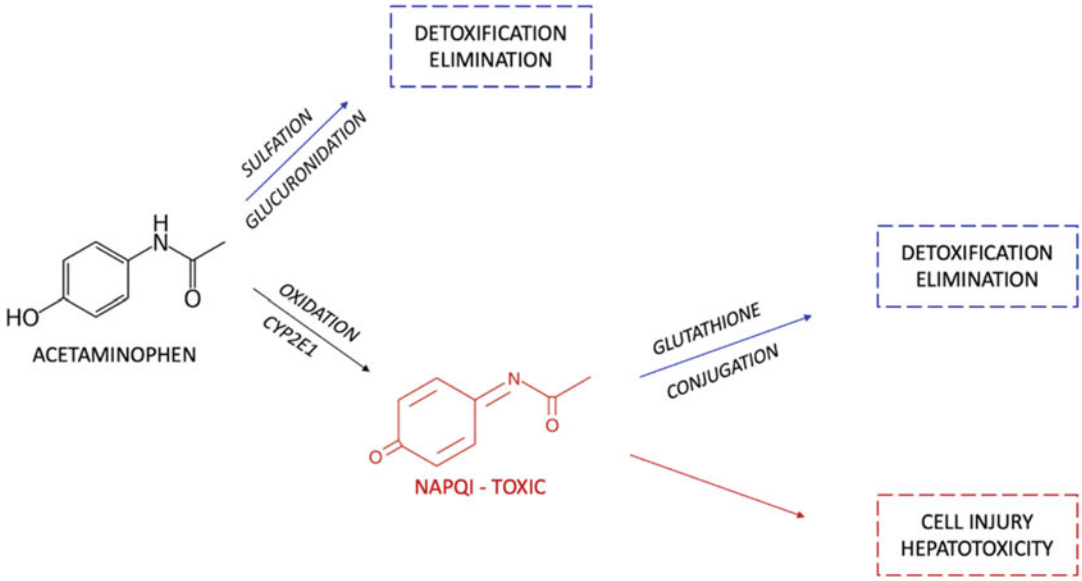


Fig. 1 Metabolism of acetaminophen

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Table 3 N-Acetylcysteine (NAC) dosing

Route	Dose
Oral	**Loading dose**: 140 mg/kg **Maintenance doses**: 70 mg/kg every 4 h for a total of 17 doses (72 h)
Intravenous	**Loading dose**: 150 mg/kg (max 15 g) in 200 mL of 5% dextrose in water infused over 60 min **Maintenance doses**: 1. 50 mg/kg (max 5 g) in 500 mL of 5% dextrose in water infused over 4 h 2. 100 mg/kg (max 10 g) in 1000 mL of 5% dextrose in water infused over 16 h *Patients weighing less than 40 kg require reduced volume administration*

Antidepressants: Tricyclic Antidepressants (TCAs)

Pharmacokinetics

TCAs exert many effects, including blocking the reuptake of norepinephrine and serotonin at the presynaptic neuron, blocking muscarinic cholinergic receptors, blocking antihistamine effect, and, to a lesser degree, blocking α-adrenergic receptors.

Clinical Presentation

Individuals with TCA overdoses may present with the following adverse effects [9]:

Cardiovascular: Hypo- or hypertension, tachy- or bradycardia, increased QRS or QT interval, atrioventricular conduction block, and complete heart block

Respiratory: Hypoventilation, crackles, and hypoxia

Neurologic: Delirium, lethargy, seizures, and coma

Other: Hyperthermia, dry mucous membranes, urinary retention, and blurred vision

Management

There are no specific antidotes for TCA overdoses and general supportive care is recommended, with a focus on airway, breathing, and circulation. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure. Administer crystalloid or colloids fluids to maintain hemodynamics.

Alkalinization of blood to a pH of 7.45–7.55 with sodium bicarbonate is recommended for the TCAs. Proposed indications for sodium bicarbonate include: QRS greater than 100–120 milliseconds, wide complex tachycardia, cardiac arrest, right bundle branch block, refractory hypotension, and serum electrolytes replacement if QT prolongation causes [10].

Sodium bicarbonate dosing is as follows:

1. Bolus dose: 1 mEq/kg (minimum 50 mEq)
2. May repeat bolus every 15 min until ECG stabilized or arterial pH goal achieved
3. May consider a continuous infusion of hypertonic saline for patients refractory to sodium bicarbonate

Seizures should be managed with benzodiazepines. Phenobarbital may be considered if the patient is refractory to benzodiazepines and has a stable blood pressure.

Antidepressants: Selective Serotonin +/− Norepinephrine Reuptake Inhibitors (SSRIs/SNRIs)

Pharmacokinetics

Serotonin syndrome is caused by excessive serotonin concentrations leading to overstimulation of serotonin-1 A and serotonin-2 A receptors in the central and peripheral nervous systems.

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Clinical Presentation

Adverse effects include altered mental status, autonomic instability (hyperthermia, tachycardia, hypertension, arrhythmias), and neuromuscular changes (hyperreflexia, increased rigidity) [11].

Management

Treatment should focus on supportive care; symptoms typically resolve within 24–48 h [8].

(a) Discontinue the offending agent
(b) Benzodiazepines should be administered as first line for agitation and muscle rigidity
(c) Cyproheptadine 8–12 mg by mouth should be administered for agitation and muscle rigidity as an adjunct to benzodiazepines

Aspirin/Salicylates

Pharmacokinetics

The mechanism of toxicity for salicylates is through the interference with aerobic metabolism owing to the uncoupling of mitochondrial oxidative phosphorylation, leading to increases in anaerobic metabolism, which causes a significant lactic acidosis. This also leads to hypoglycemia because of glycogen depletion, gluconeogenesis, and catabolism of proteins and free fatty acids.

Clinical Presentation

The most common clinical symptoms associated with a salicylate overdose are hyperventilation (respiratory alkalosis), tinnitus, and GI irritation. Symptoms may vary depending on the serum salicylate level; however, these may be low to normal early in the presentation [12]:

(a) Serum level less than 30 mg/dL: Asymptomatic
(b) Serum level 15–30 mg/dL: Therapeutic levels
(c) Serum level 30–50 mg/dL: Hyperventilation, nausea, vomiting, tinnitus, and dizziness
(d) Serum level 50–70 mg/dL: Tachypnea, fever, sweating, dehydration, and listlessness
(e) Serum level greater than 70 mg/dL: Coma, seizures, hallucinations, stupor, cerebral edema, dysrhythmias, hypotension, oliguria, and renal failure

Patients should be monitored for up to 24 h because of the possibility of delayed or impaired absorption.

Management

There is no antidote for salicylate poisoning. The goals of therapy are to limit the additional absorption of salicylates and to provide supportive care. Gastric decontamination with a single dose of activated charcoal is recommended if the patient is alert and not vomiting. Otherwise, treatment is mostly symptom management [13]:

1. Administer intravenous crystalloid fluids to maintain blood pressure
2. Administer intravenous glucose for hypoglycemia or significant neurologic symptoms
3. Urine alkalinization is recommended to enhance renal elimination and increase the glomerular filtration rate
4. Consider hemodialysis if appropriate

Opiates

Pharmacokinetics

Opioids act at the mu, delta, and kappa opioid receptors, although mu is responsible for most of the opioids' clinical effects. The most common agents associated with a toxicologic death are methadone, oxycodone, morphine, and tramadol.

Clinical Presentation

The most common clinical symptoms associated with opioid overdose are respiratory depression, coma, miosis, and hypoactive bowel sounds. Additional findings may include stupor,

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hepatotoxicity, acute renal failure, rhabdomyolysis, compartment syndrome, hypothermia, and seizures [14].

Management

Antidote therapy is recommended with naloxone. The mechanism of action of naloxone is that it is a competitive antagonist at the opioid receptor. The intravenous route is preferred, but naloxone is also effective through the intramuscular, intranasal, inhalational, or intrapulmonary route. Onset of action of intravenous naloxone is 2 min with a duration of 30–120 min. Dosing may be affected by the specific opioid agent and dose, affinity for the mu-receptor, and patient weight.

Initial dose is 0.04 mg in adult patients and 0.1 mg/kg in pediatric patients; if no response, the dose is increased every 2–3 min to 0.5 mg, 2 mg, 4 mg, and 10 mg, followed by 15 mg. It is recommended that a continuous infusion be initiated at a dose of two-thirds the effective bolus dose per hour (0.04–4 mg/h) for patients requiring subsequent naloxone doses to sustain effect.

Adverse effects are rare and may be more related to a return of sympathetic response to opioid withdrawal. If no effect is seen, consider other causes such as secondary or alternative agents [15].

Monitoring: Observe respiratory status and vital signs for a minimum of 4–6 h after the last dose of naloxone or discontinuation of the continuous infusion.

Disposition

The first priority is hemodynamic stability and airway protection of the poisoned patient. General indications to consider hospital admission include: altered mental status, persistent abnormal vital signs, and predicted delay in toxicity (in long acting/sustained release preparation ingestion). In patients who remain hemodynamically stable, have an intact mental status and airway, and in whom laboratory test results are normal, if the patient is asymptomatic after 4–6 h of observation, these patients may be discharged. However, if the ingestion was intentional, those patients require psychiatric evaluation [1].

Prevention

While management of ingested poisons in the office based is limited, the family physician has an important role in counseling and prevention. Discussing with all patients, regardless of age, the significance of poisoning and prevention is encouraged. Recommendations such a clearly labeling household products, prescriptions, drugs, their safe storage, and disposal. The family physician should proceed with caution when prescribing opioids and use nonnarcotics when possible [1].

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Care of Acute Lacerations

52

Brian Frank, Dan Stein, Carl Rasmussen, Jade Koide, and Katharine Marshall

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Introduction

A laceration is a traumatic disruption of the epidermal/dermal junction. Treatment of acute lacerations typically requires mechanical support to approximate disrupted skin layers. Assessment of lacerations should include consideration of infection risk, evaluation of nearby vital structures for damage (e.g., nerves, blood vessels, tendons, etc.), and choice of closure technique to maximize functional and cosmetic outcomes.

Skin Anatomy and Wound Healing

Skin anatomy and the phases of wound healing are important concepts for laceration repair. All skin has a keratinized epidermis with a single, basal layer of regenerative cells. Deep under this is a collagen-rich dermis overlying subcutaneous fat and muscle. The dermal layer provides the majority of skin's strength. Figure 1 represents normal skin and subcutaneous tissue anatomy.

Wound Closure

Closure of acute lacerations is called "primary closure" or "closure by primary intent." Suturing remains the most common form of primary closure; however, alternative methods (e.g., wound closure tapes, staples, and tissue adhesives) may also be used. Secondary closure or "healing by secondary intent" describes wounds left open to heal by granulation. Tertiary closure refers to delayed primary closure. Most lacerations are repaired by primary closure.

Wound healing occurs in three phases: inflammatory, proliferative, and maturation. The inflammatory phase begins at the time of injury and lasts

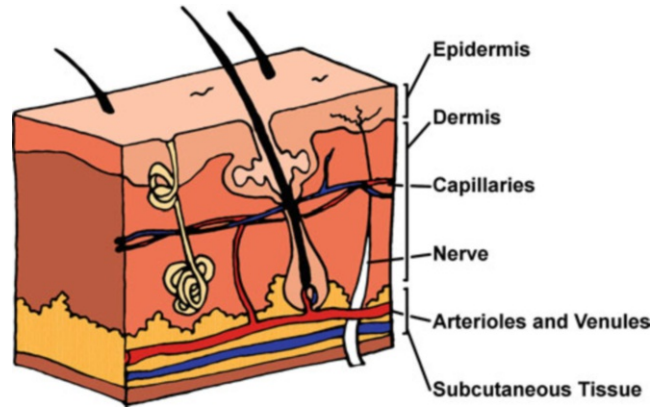


Fig. 1 Normal skin anatomy

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roughly 5 days. Once hemostasis occurs, macrophages and neutrophils remove foreign material and devitalized tissue. There is no gain in wound strength during this time. The proliferative phase occurs between days 6 and 14, during which time fibroblasts initiate collagen synthesis. By the end of this phase, disorganized collagen bundles are present but wound strength is poor [1]. Primary closure provides reinforcement during the first two phases of healing. Starting at 2 weeks after injury, the maturation phase involves remodeling of collagen bundle creation of the fibrotic scar. Everting skin edges (discussed below) help prevent inversion of the scar as it contracts. The healing process restores skin strength to approximately 80% of normal [2].

Indications/Contraindications to Primary Closure

There is debate over how soon after injury a laceration must be repaired to optimize healing. Infection rate does not increase with delayed repair; however, rate of healing appears slowed after 19 h [3, 4]. Grossly contaminated wounds, wounds that appear infected, and those with significant devitalized tissue such as crush injuries are at high risk for infection. These injuries should be left open and evaluated for tertiary closure in 72 h [5]. If the wound remains uninfected, delayed primary closure can occur at that time; otherwise, the wound should heal by secondary intent. If delayed repair is not an option, wound edges can be loosely approximated with interrupted sutures to reduce scar size and allow for drainage. The decision to repair a wound depends on the skill and comfort level of the individual provider; the following injuries should prompt consideration of specialty referral [6]:

Deep hand or foot wounds
Full-thickness eyelid, lip, or ear lacerations
Nerve, artery, bone, or joint involvement
Penetrating wounds of unknown depth
Severe crush injuries
Severely contaminated wounds requiring drainage Cosmetic outcome of significant importance

Anesthesia
Local Anesthesia
Topical Anesthesia

For patient comfort, it is preferable to anesthetize wounds prior to inspection and cleansing. Several routes of administration exist. Topical agents consist of one or more anesthetics with or without a vasoconstrictor (e.g., lidocaine/epinephrine/tetracaine). To apply, a cotton ball soaked with the topical agent is placed over the wound and covered with an occlusive dressing. Application is painless and wound margins are not distorted with application. Anesthetic effect is achieved gradually [6]. Topical agents are absorbed through subepidermal and mucosal tissue. Larger injuries may absorb a volume of anesthetic in excess of the recommended dose; caution should be used. Topical agents are a good choice for pediatric populations and can be used alone or as an adjunct to injectable agents [6]. Once the wound is anesthetized, distraction with toys or games helps minimize the patient's anxiety [7].

Injectable Anesthesia

Injectable anesthetics achieve effect more quickly than topical agents but are more painful. The most commonly used are lidocaine and bupivacaine. Onset of action is <5 min, but duration of anesthesia varies between agents. Bupivacaine lasts about four times longer (120–240 min) than lidocaine (30–60 min). Duration of action can be extended with the addition of epinephrine. Premixed formulations of anesthetic and epinephrine are commonly available [8]. Despite long-standing beliefs to the contrary, agents containing epinephrine do not increase the risk of necrosis in areas with end arterioles such as fingers and toes; in fact, the use of vasoconstrictors improves hemostasis and can reduce the need for tourniquets [7, 8, 9].

Discomfort from injection can be reduced by buffering the anesthetic with sterile sodium bicarbonate at a 10:1 ratio, injecting through the open wound to avoid nerve endings and infiltrating slowly with the smallest-gauge needle possible

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[5]. Partially withdrawing the needle and changing the angle prior to advancing ("fanning") decreases the number of injection sites. Allergies to injectable anesthesia are rare; still, patients should be asked about these prior to administration.

Injectable anesthetics can be administered by direct infiltration of the wound ("local" anesthesia), infiltration around the wound (a "field block"), or by proximal infiltration of a nerve that supplies the injured area ("nerve block"). Local anesthesia is used for simple lacerations on the face, trunk, and extremities. Field blocks (Fig. 2) are most useful for injuries where maintenance of architecture is crucial (e.g., lacerations of the ear). Nerve blocks require smaller volumes of anesthetic and last longer than local or field blocks though anesthetic effect takes longer. Additionally, they can anesthetize large areas with a single injection, a property helpful for managing large or diffuse areas of injury supplied by a common nerve. Nerve blocks require a careful review of anatomy and, due to the caliber of the targeted nerve, have an increased risk of prolonged paresthesia. The digital block pictured below is one of the most common nerve blocks and illustrates the general technique required (Fig. 3).

In patients with significant anxiety or who are otherwise unable to tolerate wound repair with local anesthetic, systemic sedation with anxiolytics, analgesics, and/or sedative hypnotics is an alternative. The use of these medications is often referred to as "procedural sedation and analgesia" (PSA). PSA can be safely utilized by family physicians and advanced practice providers but requires in-depth familiarity with the medications required, their potential complications, and the monitoring and personnel required for their use.

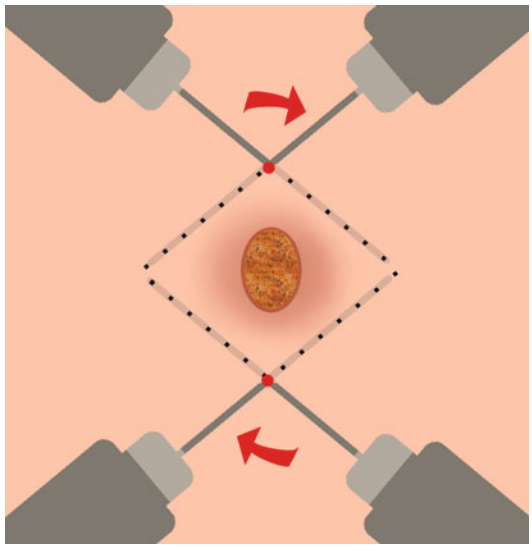
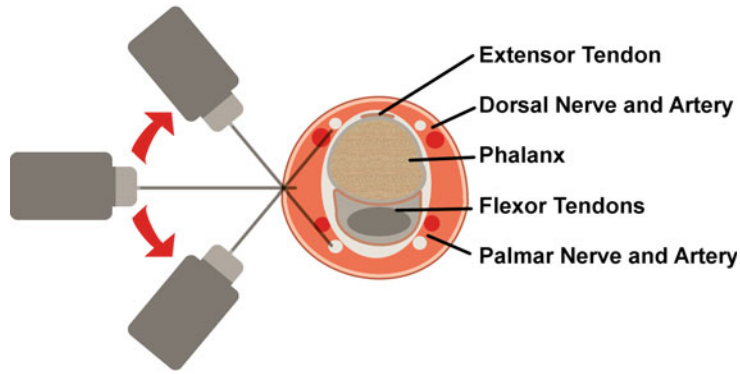


Fig. 2 Injectable anesthesia by field block

Wound Preparation and Further Assessment

The first step in wound repair is ensuring availability of the proper equipment (Table 1). Once accomplished, attention can be turned to the laceration. Now anesthetized, the wound should be inspected for debris and other foreign bodies; damage to deeper tissues; or damage to vessels,

Fig. 3 Digital nerve block



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Table 1 Equipment checklist

Patient consent form
Ruler (for billing/coding)
Anesthetic
Irrigation: 60 ml syringe, tap water, splash device
Sterile field & surgical preparation: fenestrated drape, sterile drape, povidone-iodine or chlorhexidine gluconate, alcohol swabs
Sterile gloves (not needed in uncomplicated closure) [31] Suture Needle driver Pickups with teeth (less traumatic than blunt pickups)

nerves, or tendons and specialty referral considered as needed. Once this is complete, irrigation is used to wash away debris or foreign matter and dilutes the bacterial concentration present in the wound. Tap water and sterile saline have equivalent rates of post-repair wound infection, the former being more cost effective [14]. Warmed irrigation solution is less painful. A 60 mL syringe with an 18-gauge angiocatheter supplies adequate pressure without damaging tissue [5]. Commercial splash shields protect against body fluid exposure. The optimal volume of irrigation fluid has not been adequately reported; however, most sources recommend a minimum of 250 mL [15]. Visible foreign matter remaining after irrigation should be removed with sterile forceps, using caution with removal of foreign bodies located near vessels, nerves, or tendons. Wrapping a gloved finger with petroleum-embedded gauze can help the clinician remove debris or greasy contaminants remaining in the wound after irrigation. Povidone-iodine, hydrogen peroxide, alcohol-based, or other chemical solutions may be used for cleaning skin surrounding the wound but should not be applied within the wound or approximating skin edges. These solutions are toxic to underlying tissue and impede wound healing. Hair surrounding the wound should be clipped but not shaved to avoid wound contamination. Shaving is associated with increased rates of infection [15].

Radiographs are recommended for wounds sustained from glass or metal fragments. Plastic and wood are not radiopaque, so advanced imaging should be considered if the presence of these materials is suspected.

Suture Characteristics

The most common sutures used for percutaneous closure are made from nonabsorbable, synthetic polymers such as nylon and polypropylene in a single filament. These produce less tissue reactivity than natural fibers such as silk and pose decreased risk of infection compared to braided material [16, 17]. In contrast, absorbable sutures are used to reinforce the dermis and provide hemostasis. Synthetic materials are less inflammatory than "gut" sutures made from animal connective tissue and thus are preferred (Table 2) [16, 17].

A suture's thickness is inversely proportional to the number on its package (e.g., 3-0 suture is thicker than 4-0 suture). To optimize cosmetic results, providers should choose the finest suture that will provide sufficient structural support. Generally, lacerations on the trunk are repaired with 3-0 or 4-0 suture, extremities and scalp with 4-0 or 5-0, and face with 5-0 or 6-0 [15]. Sutures are most commonly tied with a square knot. Five knots (also called "ties" or "throws") per suture provides optimal stability. In nearly all cases, a 3/8 curvature of circle on a reverse cutting needle is sufficient for laceration repair. It is easier to maneuver in small areas than a 1/2 curvature and slides through skin better than a tapered needle (Table 2).

After cleansing, the wound is draped with a sterile drape or sterile towels to create a clean field. Devitalized tissue should be debrided, and wound edges trimmed so they are perpendicular to the skin surface with slight undermining to promote eversion of wound edges (Fig. 4). Undermining permits greater mobility of the skin surface by releasing subcutaneous attachments. A scalpel or pair of sharp scissors is used to make cuts of equal depth, keeping in mind that shallower cuts pose a greater risk of compromising tissue perfusion. Greater tension occurs at the center of the wound, so this area requires the widest undermining (Fig. 5) [18]. Intradermal retention sutures that bring together dermis can reduce wound tension and approximate wound edges (Fig. 6). Absorbable suture material is typically used for deep sutures. The technique for placing deep retention sutures is similar to simple interrupted and is described below.

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Table 2 Suture characteristics

	Suture	Advantages	Disadvantages	Tissue reactivity
Absorbable	Catgut (plain)	Inexpensive	Low tensile strength and retention (7–10 days), high tissue reaction	High
	Chromic gut	Inexpensive	Moderate tensile strength, retention, and tissue reaction	Moderate
	Polyglactic acid (Vicryl)	Braided, coated, easy handling, mild tissue reaction		Low
	Polyglycolic acid (Dexon)	Good tensile and knot strength, low tissue reaction	Difficult to handle	Low
Nonabsorbable	Silk	Moderate tensile strength	Moderate tissue reaction	Moderate
	Nylon (Ethilon, Dermalon)	Low tissue reaction	Difficult to handle, need many knots	Low
	Polypropylene (Prolene, SurgiPro)	Permanent, minimal tissue reaction	Needs extra knots	Low
	Braided polyester (Mersilene, Ethiflex)		Greater infection risk relative to monofilament	Low

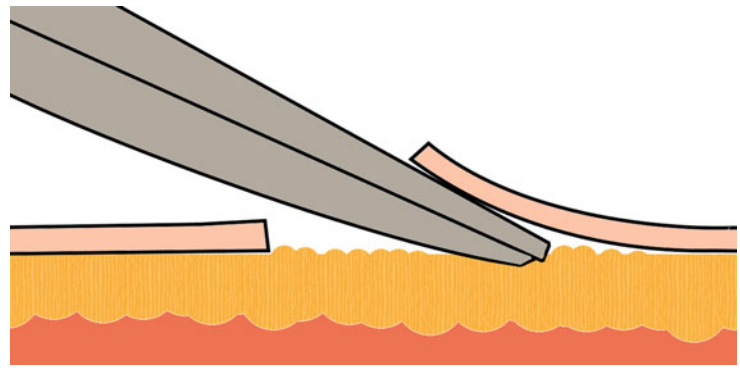


Fig. 4 Undermining wound edges, sagittal view

Various suturing techniques are discussed below. The fundamental goals for all are as follows:

1. Hemostasis: Brisk bleeding should be controlled prior to closing a wound. If direct pressure is insufficient, electrocautery or ligation of bleeding vessels with absorbable sutures may be required. Care should be taken not to cauterize the epithelium, as this will increase scarring. Attempts to cauterize capillaries may compromise blood supply and is generally unnecessary, as capillary bleeding should stop with wound closure.
2. Elimination of Dead Space: Fluid accumulation between or within tissue planes can impair healing and act as a nidus for infection. In wounds that penetrate the subcutaneous space, deep absorbable sutures are used to reduce seroma formation. The use of temporary drains (silicone or latex tubing) is of limited value and should be avoided.
3. Approximation of Tissue Layers: Sutures should approximate corresponding tissue types with enough pressure to slightly evert

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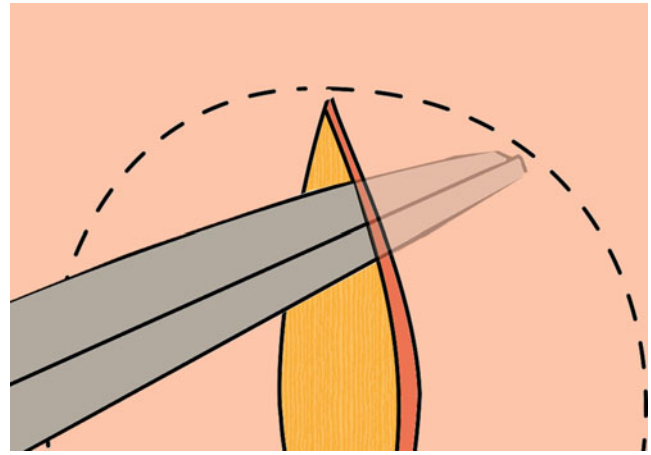


Fig. 5 Undermining wound edges

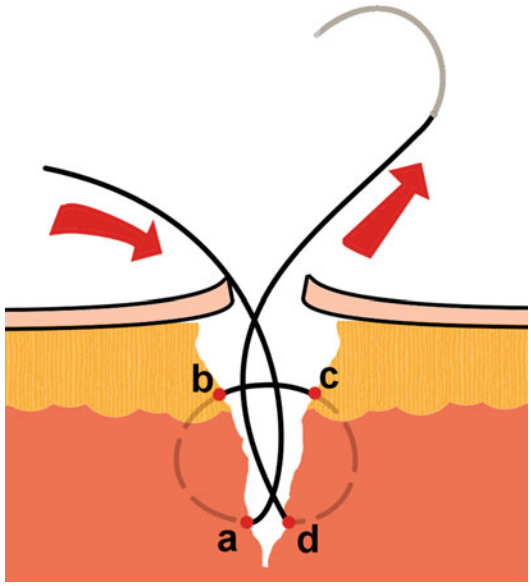


Fig. 6 Intradermal retention suture with buried knot. The suture enters the wound edge deep and, following the curve of the needle, exits superficially (still below the dermal-epidermal junction). This throw is reversed on the opposite wound edge and tied off, leaving a "buried" knot

wound edges. This ensures that keratinized epithelium does not impair healing and decreases the risk of fibrotic contraction causing a noticeable defect. Tension on wound edges should be minimized with undermining and the use of appropriate suture technique. Sutures under high tension can compromise circulation.

Simple Interrupted Closure

Simple lacerations are most commonly repaired with the simple interrupted closure. Individual sutures are placed in parallel to one another at regular intervals along the laceration to provide multiple points of tissue support. The first stitch should bisect the wound perpendicularly to facilitate a symmetric repair. Using a needle driver, the point of the needle enters the skin perpendicular to the surface and penetrates halfway through the dermis. Following the curve of the needle, the needle driver is turned 90°. The needle exits one side of the laceration and enters the other at the same depth, and the needle driver is again turned 90°. The exit point should be directly across the wound edge from the entry point. Both points should be equidistant from the wound edge. The suture should be as wide as it is deep (Fig. 7). Using an instrument tie (Fig. 8), the suture is tied tightly enough to approximate and evert wound edges but not enough to indent the epidermis. Subsequent sutures are placed in parallel (Fig. 8).

Simple Running Closure

A simple running closure can be completed quickly, an advantage in emergency situations (Fig. 9). It is useful for long, low-tension wounds but should be avoided in high-tension wounds due to the risk of circulatory compromise. Interrupted

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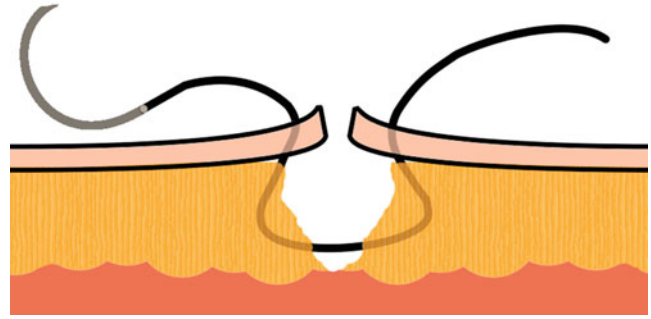


Fig. 7 Simple interrupted, sagittal view

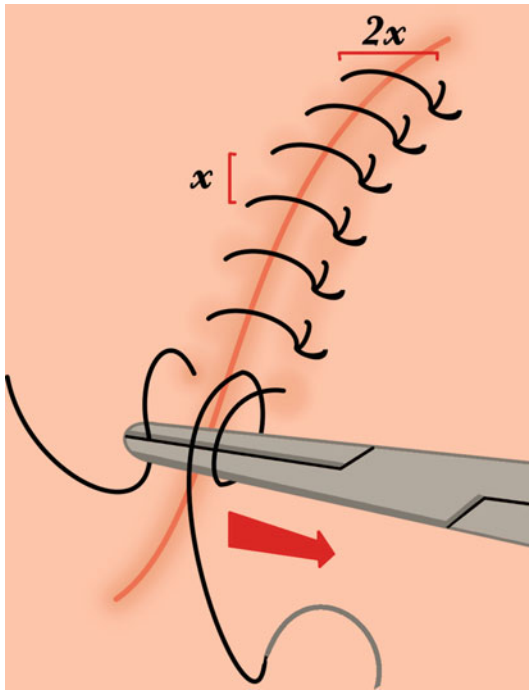


Fig. 8 Suture spacing of simple interrupted closure

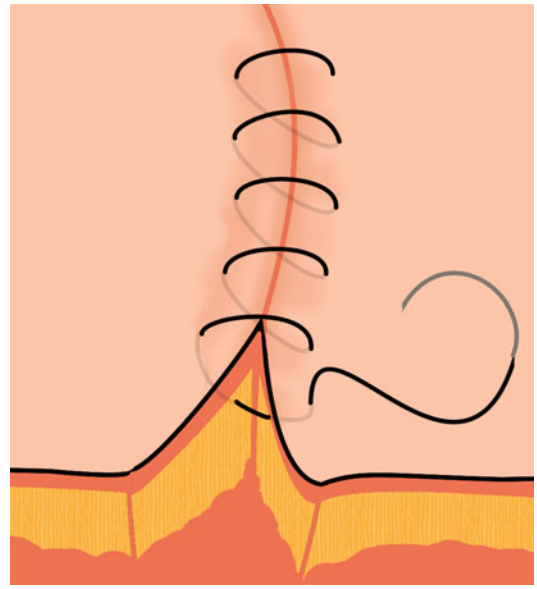


Fig. 9 Simple running closure. Symmetric "baseball stitches" are placed with a single suture and the ends are knotted. The width and depth of each bite should be equal

rather than running sutures should be used if infection risk is high to allow for selective removal of individual sutures to promote drainage without the risk of dehiscence.

Intradermal Running Closure

The term "subcuticular" refers to placement of the suture below the stratum corneum. A more apt term for this stitch is "intradermal." Intradermal sutures are accomplished by driving the needle back and forth across the laceration in parallel to the skin layers, using the dermis as an anchor. An intradermal running closure should be considered when cosmetic outcome is important, such as for facial wounds, as this method creates minimal scarring [19, 20, 21]. Intradermal sutures provide less tissue support than percutaneous sutures so should be reserved for linear, shallow wounds under minimal tension (Figs. 10 and 11).

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Buried knots are used to anchor absorbable intradermal sutures and are placed with the same technique as buried retention sutures). The important difference is, rather than cutting both tails, the end connected to the needle is then used for the intradermal closure. If nonabsorbable sutures are used, the skin is entered approximately 1 cm from the apex. Several techniques are used to complete an intradermal repair. The simplest of these is shown below (Fig. 11). Both "tails" are secured in place by adhesive strips. Once initial wound strength has occurred (typically 5–7 days), the suture is removed by gently pulling one end against countertraction.

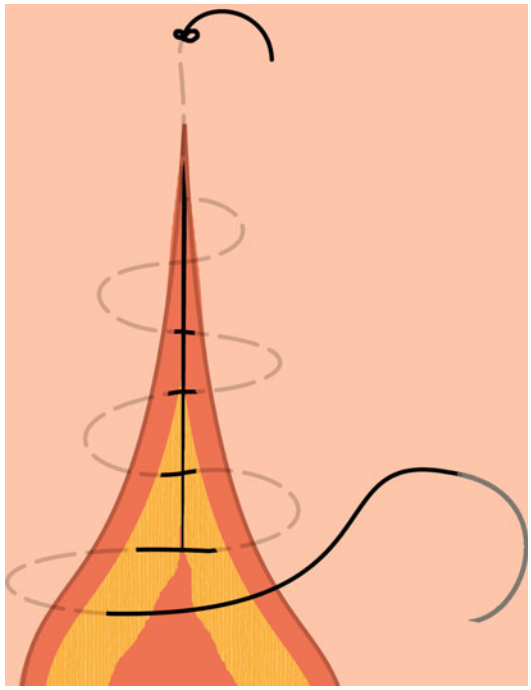


Fig. 10 Intradermal running closure. The wound is entered and exited through its apices. Horizontal "zig-zagging" passes are made with symmetric bites at the dermal-epidermal junction

Two-Layer Closure

High-tension wounds and those with significant dead space require intradermal retention sutures to approximate underlying tissue. A simple interrupted suture can then approximate the skin edges under lower tension (Fig. 12).

Horizontal Mattress Suture

In situations where intradermal sutures cannot be placed (such as palms or soles) horizontal mattress sutures should be considered for closure of gaping or high-tension wounds because they spread tension across the skin surface (Fig. 13). For this reason, horizontal mattress sutures are also useful in areas with fragile skin [6].

Vertical Mattress Suture

Like the horizontal mattress, this suture is useful in high-tension wounds. It is particularly good for injuries where skin eversion would otherwise be difficult (Fig. 14) [6].

Half-Buried Mattress Suture

Half-buried mattress sutures, (a.k.a. "corner stitches") are used to close stellate or triangular lacerations without impairing blood flow [6]. Two

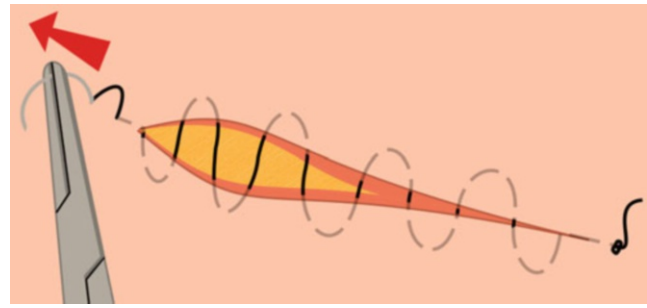


Fig. 11 Completion of intradermal closure. The needle exits the skin approximately 1 cm from the apex and is pulled taut to approximate wound edges. It is then cut 1–2 cm from the skin and the tail secured by adhesive strip

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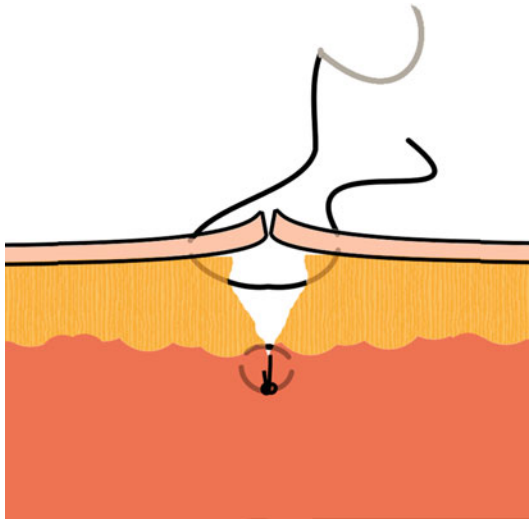


Fig. 12 Two-layer closure. A buried intradermal retention suture placed deep to a simple interrupted suture. Note the area of undermining just below the epidermis

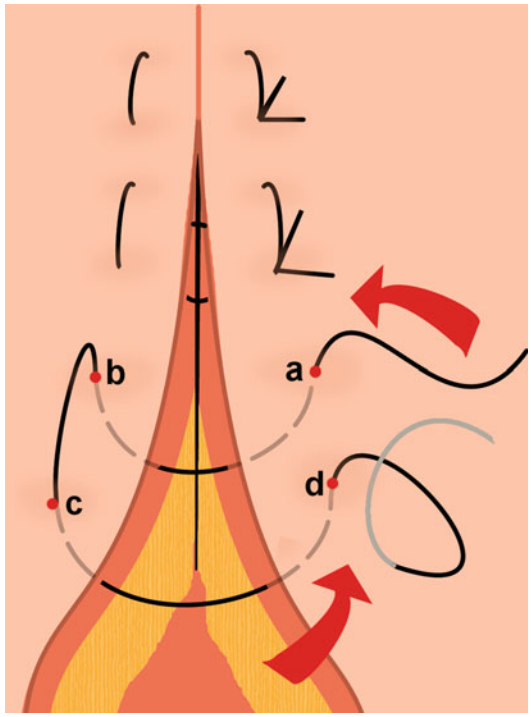


Fig. 13 Horizontal mattress suture. The needle enters 0.5–1 cm from the wound edge, passes deep into the wound and exits symmetrically at the opposite side. The needle reenters and is passed in parallel to the first suture and exits the skin. The knot is then tied in parallel with the wound

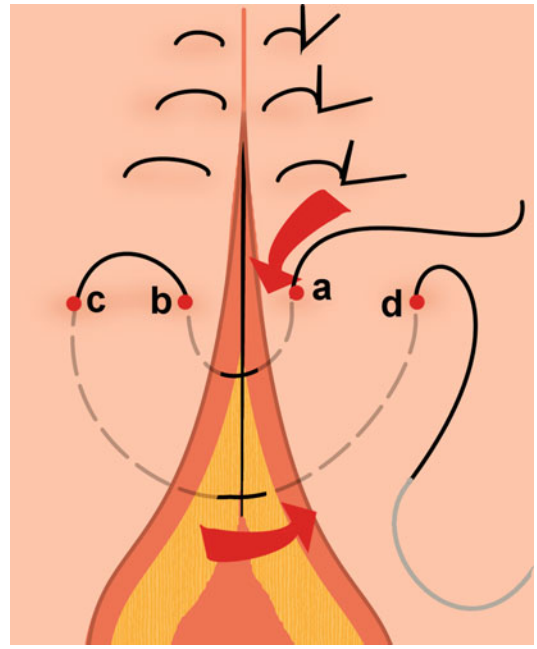


Fig. 14 Vertical mattress suture. The needle enters 0.5–1 cm from the wound edge, passes shallow and exits symmetrically at the opposite side. The needle then reenters laterally on the same side, enters deep into the wound under the previous suture and exits directly lateral to the initial entrance site. The knot is tied perpendicularly with the wound

variations of this technique are illustrated below (Figs. 15 and 16).

Dog-Ear Repair

Wound edges of unequal length (e.g., an arcuate laceration) often result in excess tissue on the longer edge at the end of the repair. Figure 17a–c demonstrates a technique for removing these "dog ears" to improve cosmetic outcomes.

Alternatives to Sutures

Sutures are not always indicated for minor lacerations. Most alternative means of wound closure take less time than suturing, and many are less painful and invasive; however, not all provide satisfactory outcomes when compared to suturing. Alternative

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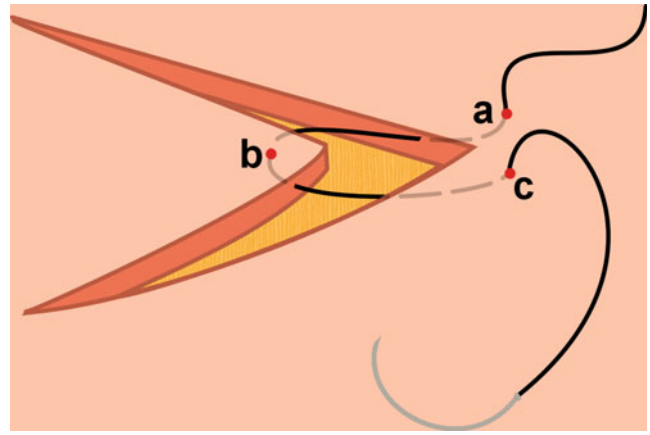


Fig. 15 V-flap repair

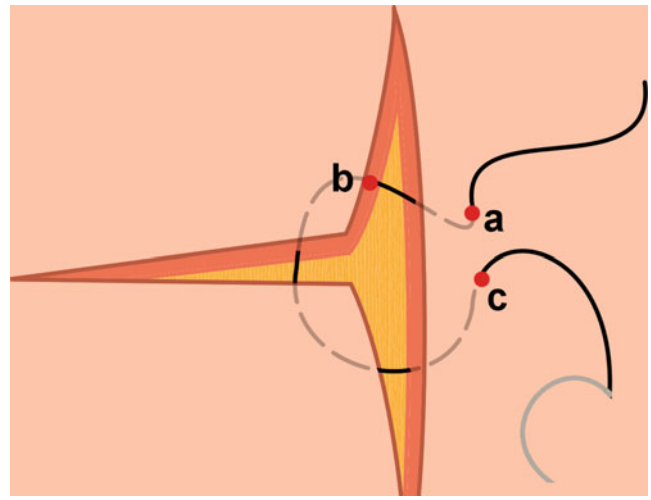


Fig. 16 T-laceration repair

wound closures fall into one of two categories: tissue adhesives and percutaneous staples.

Tissue Adhesives

The most commonly used tissue adhesives are derivatives of commercially available cyanoacrylate glues (e.g., "Krazy Glue®" or "Super Glue®") but are less histotoxic. Adhesives are sold in liquid form and come in a variety of applicators, all with the same function. Wound edges are approximated, and adhesive is applied in a thin layer and allowed to polymerize. Typically, three coats are applied creating a waterproof, antimicrobial barrier. For linear, low-tension, traumatic lacerations, cosmetic outcomes between adhesives and sutures are comparable, as are rates of infection though there is greater chance of dehiscence with adhesives [22, 23]. Sutures are more appropriate to repair infected, heavily contaminated, or devitalized wounds as well as those crossing mucocutaneous junctions and joint lines. Proper application of tissue adhesives requires the following:

Wounds should be clean, dry, and hemostatic. (Areas with high moisture such as the groin and axillae should be avoided.)

Edges should be closely approximated and in areas with minimal tension. Intradermal sutures may be used to reduce wound tension.

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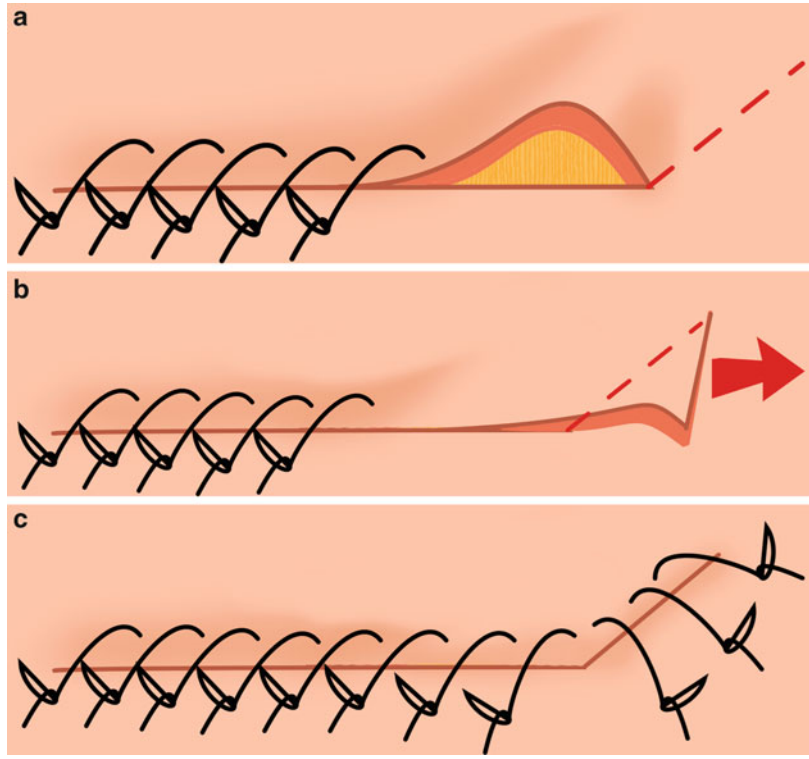


Fig. 17 Dog-ear repair 1–3. (**a**) Incise along the bulging dog ear to free the skin. (**b**) Pull freed skin edge and excise excess skin. (**c**) Close the new incision to allow skin to lie evenly

Wounds should be parallel with the floor to prevent adhesive runoff.

For scalp lacerations, the use of hair apposition (applying adhesive to the wound and then twisting together hair from opposite sides of the wound edge) provides better cosmetic outcomes than suturing with decreased pain and healing times [24]. Use of adhesives on complex lacerations (e.g., stellate, jagged edges, devitalized tissue, contaminated) is not appropriate. Care should be taken to avoid introducing adhesive into the wound as this will delay healing and may cause inflammation. Adhesive runoff into crevices or mucous membranes (especially eyes) is to be prevented. Petroleum-based products degrade adhesives, risking dehiscence. The advantages of adhesives over sutures include shortened procedure duration and decreased procedural pain.

Staples

Like tissue adhesives, staples require comparatively less time to apply than sutures. Unlike tissue adhesives, staples provide adequate support to wound edges in high-tension areas and are an appropriate alternative for more complex lacerations. Infection rates favor the use of staples, even in contaminated wounds [25, 26]. Due to concerns for poor cosmetic outcome, staples have not been compared to sutures for facial lacerations and are generally contraindicated as such; however, healing time and cosmetic outcomes with staples in comparison to sutures appear to be statistically similar for lacerations elsewhere on the body [25, 26]. Staples are safe in magnetic resonance imaging (MRI); however, they may cause interference with images in MRI and computed tomography (CT) studies. Timing of removal is the same as for sutures but requires the use of a surgical staple remover.

Adhesive Strips

Adhesive strips (typically a porous tape reinforced with polyester fibers) are most suitable for maintaining wound edge approximation after the removal of sutures in wounds that have not completely healed. They can also be used for small lacerations with very low skin tension in

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areas that are relatively hairless and will not become wet. Other applications are unsuitable. Generally, using a styrax resin-derived adhesive product (e.g., tincture of benzoin, mastisol) can help the strips adhere to the skin longer. As with tissue adhesives, care should be taken to avoid these adhesives from entering wounds.

Antibiotics

As a general rule, prophylactic antibiotics do not decrease rates of infection and should not be used [27]. In certain high-risk situations, however, antibiotic prophylaxis is warranted. These situations are

Patients with immunocompromise
Wounds exposing fractured bone ends, joint spaces, tendons, or cartilage wounds in which gross contamination cannot be removed
Puncture wounds (due to inability for adequate irrigation)
Crush injuries with extensive devitalized tissue, bite wounds
Wounds in the mouth
Wounds occurring >18 h prior to presentation [27]

Prophylactic antibiotics should target the most likely contaminating organisms. For most wounds, a first- generation cephalosporin provides sufficient coverage. Coverage for methicillin-resistant staphylococcus aureus (MRSA) should be considered but is not generally necessary unless the patient has a personal history of or close contact with MRSA infection. Patients with oral wounds should receive penicillin. There is a range of potential contaminants arising from specific exposures that should be considered including exposure to farm animals or marine environments and bite wounds. Specific treatments for these scenarios are discussed elsewhere [27]. Topical triple-antibiotic ointment appears to decrease infection rates in contaminated wounds compared with white petrolatum; however, these differences are not seen with sterile or clean wounds [28]. Tetanus prophylaxis should be considered as outlined in the table below (Table 3).

Table 3 Tetanus prophylaxis

	Clean, minor wounds		All other wounds	
Vaccination history	Td[a]	TIG	Td	TIG
Unknown or <3 doses	Yes	No	Yes	Yes
>3 doses	No[b]	No	No[c]	No

[a]Can use TdaP if patient is >10 years old and has not previously received TdaP
[b]Yes if >10 years since last dose
[c]Yes if >5 years since last dose

After the wound has been appropriately repaired, every effort should be taken to ensure that patients understand all instructions for wound care, monitoring for complications and, if indicated, dose, route, and timing of antibiotics. Patients should be advised to watch for signs of infection such as cloudy (purulent) drainage, increasing redness around the wound, unexpected pain, red streaks leading from the wound toward the trunk, fever, or increasing swelling of the wound >24 h after repair.

Epithelialization is not complete until after 48 h although infection from contaminants decreases significantly by 12 h post closure. The standard recommendation is to keep wounds dry and covered for the first 24 h; however, shorter times are not clearly contraindicated [29].

Wounds heal better in moist environments [29]. Patients with clean wounds closed with sutures should be advised to apply a thin layer of white petrolatum several times per day to maintain moisture. Those with contaminated wounds should do the same with triple-antibiotic ointment. Wounds closed with adhesives should not be covered in petrolatum as this may hasten breakdown of the adhesive. Application of hydrogen peroxide, iodine, or topical astringents should be discouraged as they can impair healing.

The decision of how long sutures remain in place before removal needs to balance risk of scarring with risk of wound dehiscence. There is sufficient tensile strength in a sutured wound at 7 days following a repair to safely remove sutures from most locations. Sutures in areas under higher tension (e.g., soles of feet, extensor surfaces) should stay in place for up to 14 days while those in cosmetically sensitive areas under low tension (i.e., face) should be removed after 5 days to minimize scarring. Once sutures have

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been removed, adhesive strips can be applied to assist with wound edge approximation [3].

Pain tolerance varies widely among individuals; however, over-the-counter analgesics should provide adequate pain control for most simple lacerations. Lacerations associated with crush injuries or with exposure of bones, tendons, joints, or nerves may require short-term opiate analgesics. The judicious use of these agents is at the prescriber's discretion, and risk for chemical dependence or abuse should be evaluated at the time of medication prescribing.

Coding and Billing

Laceration repairs are billed as simple, intermediate, or complex. Wounds may be closed with sutures, staples, or tissue adhesive. The use of adhesive strips alone does not qualify as a laceration repair. Simple repairs require standard debridement ("The removal of foreign material and/or devitalized or contaminated tissue from or adjacent to a traumatic or infected wound until surrounding healthy tissue is exposed [32]."") and no more than a single-layer closure. Intermediate wounds either require two layers of closure (subcutaneous, but not fascial, and epidermal) or, for single-layer closures, require extensive cleaning or removal of particulate contaminants. Complex wounds require "more than layered closure; scar revision, debridement (e.g., traumatic lacerations or avulsions), extensive undermining, stents, or retention sutures may be required. Necessary preparation includes creation of a defect for repairs (e.g., excision of a scar requiring a complex repair) or the debridement of complicated lacerations or avulsions [30]." In addition to these criteria, wounds are categorized by length (cm) and area of the body of the laceration. A complete list of CPT codes is beyond the scope of this chapter, but the following general categories may be useful (Table 4):

Table 4 General coding for wound care

Simple wounds	CPT 12001–12021
Intermediate wounds	CPT 12031–12057
Complex wounds	CPT 13100–13160
Wound debridement	CPT 11010–11044

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Selected Injuries

53

James Hunter Winegarner

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What do drowning, barotrauma, burns, swallowed foreign bodies, and fishhook removals have in common? They are all conditions that an astute family physician should be prepared to manage. Injuries as a whole represent the fifth third leading

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Table 1 Causes of injury deaths in the USA in 2017 [1]

2017 injury deaths, USA	
All injury/ accidents	243,039
Poisoning	75,354
Motor vehicle traffic	38,659
Firearm	39,773
Fall	37,587
Drowning	4,508

cause of death in the USA by the Centers for Disease Control's (CDC) most recent Vital Statistics Report [1]. The most common causes of injury deaths are listed in Table 1.

Many of the topics covered in this chapter may present as an impromptu emergency which a family physician may encounter while working in an emergency room (ER) or urgent care clinic or even off duty. Being familiar with these injuries illustrates how a family physician is often expected to be a "jack-of-all-trades."

Drowning and Submersion Injury

General Principles

Definition/Background

Drowning and its many associated terms have been a source of confusion in the past, and in recent years there has been an effort to be more precise in the medical use of these terms. A submersion injury is a nonspecific term that encompasses any medical sequelae related to being submersed in a liquid medium. The terms near drowning, wet drowning, or dry drowning are often misused, can be misleading, and should be avoided. Improper use of these terms also leads to difficulty collecting epidemiologic data for studies. The World Health Organization (WHO) has clearly defined drowning as "the process of experiencing respiratory impairment from submersion/immersion in liquid." Furthermore, drowning outcomes should be classified as death, morbidity, and no morbidity [2, 3]. This will be the definition used in this chapter.

Submersion involves the head being under the surface of a liquid, whereas an individual may also drown while immersed (head out) in choppy or turbulent liquid. Drowning victims suffer respiratory failure due to aspiration of water into the lungs or vocal cord spasm creating airway obstruction. Both of these pathophysiologic causes of drowning lead to hypoxia, secondary cardiac arrest, and death if the drowning process is not arrested [3]. While water is by far the most common medium to cause drowning, curious readers are encouraged to research the London Beer Flood and the Boston Molasses Disaster as examples of other fatal liquids.

Epidemiology

Drowning is a leading cause of unintentional death worldwide and is especially prevalent in children who are at the highest risk of drowning [4]. Females have much lower rates of drowning compared to age-matched males. Males have a bimodal drowning risk that sees a second spike in drowning at puberty and persists well into the 30s indicating that the risk-taking behavior of young adult males (what might be called the "show-off" stage of male life) contributes to increased drowning rates (see Fig. 1).

Approach to the Patient

History

The diagnosis of drowning is not difficult given the circumstances under which these patients present. A drowning victim will present acutely with respiratory complaints. Key historical questions to ask include the following: how long were they submersed, what were they submersed in, what resuscitation has been done prior to their arrival, and what was the temperature of the water? Inquire about symptoms of shortness of breath, chest pain, and cough.

Physical Exam

The primary survey in a drowning patient follows the basic life support (BLS) and advanced cardiac life support (ACLS) guidance discussed below. Once the patient has been resuscitated and stabilizes, the physical exam should focus on the airway and lungs as these are the most affected by drowning. Crackles, rales, and wheezing may be

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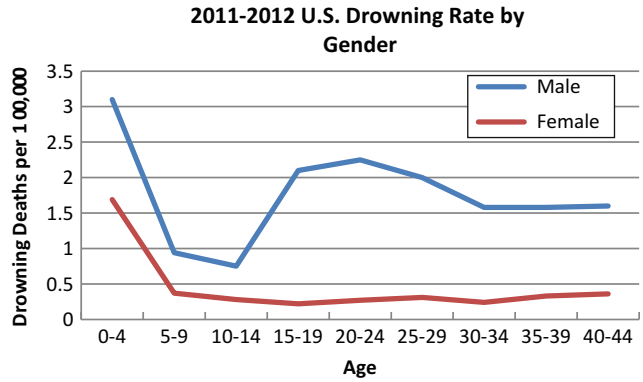


Fig. 1 US drowning death rates by age and gender, 2018 [5]

heard as the lungs often have residual edema and atelectasis due to loss of surfactant. Consider C-spine injury and immobilization if the drowning victim was in a river with white water or if they dove into shallow water [3]. Temperature is important as many drowning victims are also hypothermic due to conductive heat loss in the water. Additionally, a cold-water drowning victim can be resuscitated after extended periods of hypoxia because of decreased metabolic and oxygen requirements in hypothermia.

Treatment

First and foremost, a drowning victim needs to be removed from the water. If a patient is actively drowning, it is recommended that bystanders attempt a rescue from land or boat by throwing a flotation device or reaching with a pole or long tree branch [3, 6]. Untrained rescuers put themselves at great risk of drowning themselves if they attempt to rescue a drowning patient.

After a drowning victim is removed from the water, the patient's level of consciousness and breathing needs to be rapidly assessed. A patient that is not breathing can be assumed to have respiratory failure and possibly secondary cardiac arrest. These patients can respond to rescue breaths alone. A drowning patient that is not breathing should have their airway opened and five rescue breaths before addressing circulation [3, 6]. This is a rare exception to the current BLS algorithm which emphasizes circulation and chest compressions over airway and breathing (CAB). An unconscious patient that is breathing and has a pulse can be supported by being placed on their side in the recovery position and given supplemental oxygen, if available, while awaiting transfer to a hospital. The aspiration of fluid into the lungs washes away the surfactant [7], so patients have difficulty maintaining ventilation and may require positive pressure support to keep the alveoli open.

Evacuation to a hospital for further evaluation and monitoring should be considered in all drowning patients. Delayed respiratory failure and acute respiratory distress syndrome (ARDS) can occur as a result of surfactant loss. The severity of the patient's initial condition as well as their response to treatment will determine the length of time they need to be observed in the emergency room (ER) or as an inpatient.

Prevention

Prevention of drowning can be accomplished with adequate safety measures. Children are at the highest risk of drowning and should be the focus of prevention. Pools should be isolated with fencing (four sided and at least 4 ft. tall), and children should be supervised by an adult that is within arm's reach [8, 9]. Infants and toddlers have heads that are heavy relative to their bodies and should not have access to water in buckets or toilets because they cannot self-extricate if they fall into these head first [9]. Safety around the water should be taught at a young age, and swimming lessons are encouraged when age appropriate,

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potentially as early as 1 year old according to the American Academy of Pediatrics (AAP) [9]. Alcohol and drug use should be discouraged when around water as this contributes to the increased risk-taking behavior and increase in drowning fatalities seen in young men.

Barotrauma

General Principles

Definition/Background

Barotrauma is caused by the expansion and contraction of gas in confined spaces in and around the body. This property of a gas is driven by Boyle's law which states that at a constant temperature, the volume and pressure of a gas are inversely proportional. This law comes into effect when humans choose to dive underwater (increase barometric pressure) or travel to high altitudes (decrease barometric pressure). Pressure increases the further down a diver goes, causing the volume of gas to shrink. It takes only 10 m (33 ft) in depth underwater to double the barometric pressure of sea level, also referred to as 1 atmosphere absolute (ATA). Going from 1ATA to 2ATA will half the volume of a gas. Conversely, when traveling to high altitude such as in an aircraft, pressure decreases causing gas to expand; however, because water has more mass than air, it takes a much greater change in altitude to cause significant change in gas volumes. The changes in pressure and concordant changes to the volume of air confined in our body are most commonly felt as pressure in the ears [10]. Our bodies can equilibrate this pressure/volume change to some extent; however, when changes occur rapidly, such as a sudden ascent from a scuba dive or a rapid decompression of an aircraft cabin, it can cause severe or, in some cases, fatal injury.

The body has potentially confined gas in the lungs, gastrointestinal (GI) tract, middle ear, and sinuses. Rarely, teeth with a history of dental work can have confined air within a tooth. Expanding on the concepts described above, when a diver ascends from a depth of 10 m (33 ft. or 2ATA) to the surface (1ATA), the volume of air in the lungs will double. Rapid expansion of air in the lungs against a closed glottis can cause the most severe forms of barotrauma: pneumothorax, pneumomediastinum, or arterial gas embolism (AGE). For this reason, divers are taught to surface slowly while exhaling. Pneumothorax and pneumomediastinum are both caused by the expansion of gas dissecting into the pleural space or mediastinum, respectively. AGE is caused when the expanding air dissects into the pulmonary capillary beds and introduces air emboli into the circulation. Sudden cardiac arrest may occur in about 5% of AGE victims due to filling of the cardiac chambers and great vessels with air [10].

The GI tract generally has the capacity to deal with expanding gas, however, rarely; GI gas can cause intestinal rupture, especially in individuals with a history of bariatric or other gastric surgeries [10].

The middle ear is susceptible to both increased and decreased pressure, and "ear squeeze" is the most common form of barotrauma seen in divers [11]. As pressure increases, such as diving deeper underwater, the volume of gas in the middle ear decreases, and divers must Valsalva to force more air into the middle ear and maintain equilibrium. As a diver surfaces, this middle ear gas expands, and the pressure is released through the Eustachian tube. If a diver has swollen Eustachian tubes from an illness or seasonal allergies, it may lead to middle ear injury in the form of blood and engorged tissue behind the tympanic membrane (TM) or TM rupture. TM rupture causes sudden relief of pain; however, it can also cause vertigo, disorientation, and panic which are not ideal when diving. The round window of the inner ear can also rupture secondary to barotrauma; however, this is uncommon [11]. This will present with tinnitus, vertigo, and hearing loss.

The sinuses are also typically able to equilibrate pressure changes; however, in the setting of clogged sinus tracts, trapped air can cause engorgement and hemorrhage of the sinus lining. This can lead to headache and epistaxis.

Lastly, the skin may be affected by dry suits that contain trapped air or scuba masks that a diver fails to equilibrate. Many of these effects can be seen in relatively shallow water as the contraction

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and expansion of air are most dramatic in the first 10 m (33 ft) of diving.

Forms of barotrauma caused by waves of high and low pressure as seen with explosions and barotrauma due to mechanical ventilation are beyond the scope of this chapter. Additionally, scuba diving problems caused by dissolved gases, such as decompression sickness (DCS, aka "the bends") and nitrogen narcosis, are not covered in this chapter.

Approach to the Patient

Diagnosis

History

Patients presenting with barotrauma will have a history of recent exposure to scuba diving or, less commonly, high altitude with rapid decompression. Ask the patient how deep and how long they were down, how much diving they have been doing in the past few days, and how quickly they came up. Ask when the symptoms developed, on the descent or the ascent. Identify if they were doing scuba with compressed air or just breath holding. Identify where their symptoms are. Evaluate for symptoms of chest pain, shortness of breath, pleuritic pain, ear pain, bruising, skin crepitus, or epistaxis. Also, inquire about headache or focal neurologic findings. Gather a full medical history being sure to document any pulmonary disease, scarring, or previous diving injury as these can increase the risk of pulmonary barotrauma.

Physical Examination

A patient with suspected barotrauma has certain areas that must be examined. Look at the face and identify if there is any evidence of mask squeeze, which will be evident as ecchymosis on the face in the distribution of a diving mask and subconjunctival hemorrhages. Examine the ears for blood or fluid in the middle ear, dilated vessels in the TM, TM rupture, or small capillary rupture within the TM that have the appearance of red petechiae. Check the patient's hearing using the whisper test. Palpate the patient's frontal, maxillary, and ethmoid sinus regions for pain. Check cranial nerves, and perform a gross sensation, motor, and reflex exam to identify any focal neurologic findings. Auscultate the lungs listening of decreased lung sounds that could indicate a pneumothorax. Feel for crepitus in the neck indicative of subcutaneous air. Do a full abdominal exam, especially in patients with a history of abdominal surgeries. Examine the skin for ecchymosis due to "suit squeeze."

Laboratory and Imaging

In patients with suspected pulmonary barotrauma, obtain PA/LAT chest radiographs to identify pneumothorax or pneumomediastinum. Portable ultrasound is also a validated modality and highly sensitive and specific for detecting pneumothorax. Brain imaging with MRI is indicated in patients with suspected AGE; however, it should not delay treatment. Formal audiology testing should be considered for suspected middle or inner ear injury to document any hearing loss. Lastly, CT scan of the abdomen should be considered if there is concern for intestinal perforation.

Treatment

Treatment for barotrauma is based on the affected area. For skin barotrauma such as "mask squeeze," no specific treatment is necessary, and symptoms will resolve with time. For middle ear barotrauma, patients benefit from oral and nasal decongestants to establish normal Eustachian tube function as well as analgesia as needed. As long as no infection develops, TM rupture secondary to middle ear barotrauma will heal without complication [12]. Subspecialty consultation should be considered in patients with suspected inner ear barotrauma. Sinus barotrauma is treated with oral and nasal decongestants and pain medication as needed. GI barotrauma with perforation requires surgical evaluation.

Pulmonary barotrauma to include pneumomediastinum, pneumothorax, and AGE is managed as an emergency and should be transported without delay to an emergency room, preferably at a facility with a hyperbaric chamber. These

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conditions should be managed using the BLS and ACLS algorithms. The Divers Alert Network (DAN) at +1–919–684-9111 provides an international emergency hotline 24 h a day to provide first aid recommendations, evacuation assistance, and referral to the nearest hyperbaric chamber. These patients need to be monitored frequently paying close attention to respiratory status and pulse oximetry. The patient should be placed on 100% oxygen by mask if available in the prehospital setting. Administration of 100% oxygen has the intended purpose of hastening extra-alveolar gas resorption and minimizing ischemia caused by gas emboli [12]. A pneumothorax can progress to a tension pneumothorax manifested by hypotension, distended neck veins, and tracheal deviation away from the involved side. This medical emergency should be treated with urgent needle decompression of the affected side. This is accomplished using a large bore (16 gauge) needle of at least 3 in. in length inserted at the midclavicular line in the second intercostal space. Tension pneumothorax patients temporized with needle decompression will eventually need a thoracostomy tube inserted once they are at the appropriate level of care. Cases of AGE should be treated in a hyperbaric chamber as soon as possible to repressurize the patient and attempt to shrink gas emboli while the body resorbs them. Hyperbaric treatment should still be sought even if a delay in care occurs as case reports have shown improvement in patients with cerebral gas emboli as far out as 60 h [13]. Hyperbaric treatments follow the Navy treatment tables and can be repeated as necessary.

Prevention

Individuals should undergo a physical exam and clearance by a licensed provider before participating in scuba diving in order to screen for pulmonary disease such as chronic obstructive pulmonary disease (COPD) which increases the risk for pulmonary barotrauma. Prevention of barotrauma in divers can be accomplished by descending and ascending in a gradual controlled manner. A diver may need to stop changing depth to equilibrate pressure in the middle ear using a Valsalva technique as well as equilibrating the pressure within the face mask. When ascending, divers need to be sure to exhale slowly to prevent pulmonary barotrauma.

Burns

General Principles

Definition/Background

Every family physician will see patients with burns at some point in their career, and most burns may be managed on an outpatient basis. The intent of this chapter is to provide a basic understanding of burns and some clinical pearls to identify patients that can be managed in clinic and those that should see a burn specialist.

Burn terminology has changed over the years, and they are currently classified as superficial, partial, or deep. Nearly everyone has experienced a mild superficial burn at some point after being exposed to the sun for too long or touching a hot stove on accident. These burns involve the epidermis and can be extremely painful. Usually, they are self-resolving with minimal risk for complication, and lotion or aloe vera can be used to treat symptoms. The remainder of this section will cover the more severe partial- and full-thickness burns that will require more extensive medical care and knowledge.

Partial-Thickness Burns

The depth of involvement for a partial-thickness burn extends through the epidermis and some of the dermis. As the name suggests, it does not extend through the dermis into the subcutaneous layers. The partial-thickness burn is further subdivided into superficial and deep partial-thickness burns as deep partial-thickness may require surgical debridement much like full-thickness. However, burn surgeons are much more concerned with a primary care doctor's ability to differentiate between partial- and full-thickness burns. Partial-thickness burns will still have sensation on exam and are incredibly painful. The pain can be viewed as a good thing (for the provider) because

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it is one of the main clinical differentiators to use when diagnosing a burn as partial-thickness. Partial-thickness burns will often present with large friable bullae and blistering with surrounding erythematous, moist, weeping skin; however, blisters may be absent at initial presentation and develop later. Another physical finding is blanching erythema, which is absent in full-thickness burns.

Full-Thickness Burns

Full-thickness burns extend through the entire dermis and may involve deeper layers such as subcutaneous fat, muscle, tendon, or bone. Signs of full-thickness burns include lack of pain or sensation and a waxy, leathery, or charred appearance. The patient will also likely have some areas of partial-thickness burns around the areas of full-thickness burning.

Approach to the Patient

A detailed history of the injury needs to be taken when a burn patient initially presents. Pertinent things to ask are what caused the burn (thermal, flash, grease, chemical), when it occurred, was there a fire that may have caused airway involvement or CO poisoning, and what the patient has done to treat the burn so far. Additionally obtain date of last tetanus shot to identify those needing a booster.

Physical Examination

Burns should be managed as a trauma patient with a primary survey to evaluate for life threats followed by a secondary survey that includes a head to toe evaluation. Avoid the pitfall of focusing on the burn before managing an airway issue or active bleeding. The burn areas need to be exposed and the full extent of the burn needs to be documented. A major step is determining the percent of total body surface area (%TBSA) involved as this will play a part in referring the patient to the appropriate level of burn care and assist with resuscitation. Document the shape of the burn in cases involving children and consider child abuse. Suspicious patterns seen in child abuse include isolated lower body burns or circumferential burn to an extremity suggesting immersion into hot water, burns in the shape of an iron or curling iron, circular burns from cigarettes, or scarring from previous burns.

The burn needs to be identified as thermal or chemical as a chemical burn requires neutralization as well as proper protection for the provider. Additionally, an astute provider will need to consider compartment syndrome that can develop under full-thickness burns as a result of eschar formation and resultant loss of skin elasticity. If there is any concern for compartment syndrome, a family physician should obtain an urgent referral for surgical evaluation as these patients may require escharotomy.

Determination of Percent Total Body Surface Area (%TBSA)

Only partial- and full-thickness burns should be included in the estimation of %TBSA involved. The two classic teachings to help a provider determine %TBSA are the rule of nines and the 1% hand rule. The rule of nines divides the body into sections that are roughly 9% TBSA as seen in Fig. 2. Keep in mind that the rule of nines is not as accurate with children and infants due to their larger proportioned head and relatively smaller limbs. Another accepted method to determine % TBSA is the 1% hand rule. The palmar surface of the patient's hand represents roughly 1% TBSA for that patient. The patient can usually hold their hand close to the involved area to help to estimate the %TBSA. For burns involving most of the body, measure the unaffected area and subtract this from 100 to get %TBSA. This rule holds true in children as well.

The area involved needs to be addressed because a small localized full-thickness burn from a dropped crack pipe is not as concerning as a deep partial-thickness burn that extends over joints of the hand or involves the face (although cigarettes or crack pipes are concerning for different reasons). Most burn centers provide guidance on who should be referred for evaluation based on both %TBSA and location of the burn. Recently, a consensus statement published the following guidance on burn center referral criteria:

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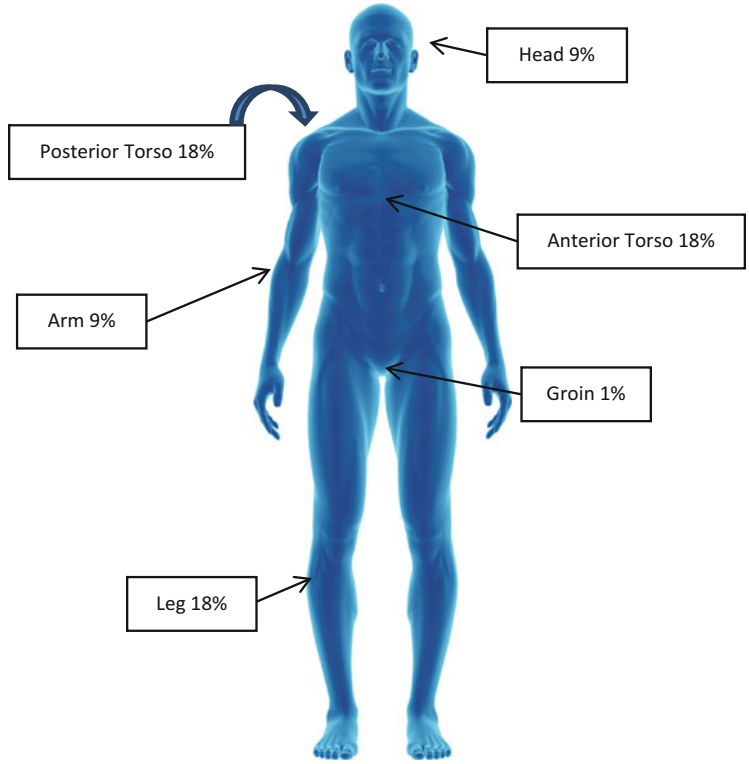


Fig. 2 Rule of nines to estimate %TBSA of partial- and full-thickness burns (Image created with adaptation of Microsoft Office© clip art)

1. Partial thickness >10% TBSA or full thickness >5% TBSA, children or elderly, or electrical/chemical/radiation
2. Smaller burns referred to outpatient burn center within a week
3. Frostbite, toxic epidermal necrolysis/Stevens-Johnson syndrome (TENS/SJS), or necrotizing fasciitis
4. Consider telemedicine if available to assist with assessment and referral guidance [14]

Treatment

Partial-Thickness Burn

The main principles for initially managing partial-thickness burns involve pain control, determination of %TBSA involved, prevention of infection, and fluid resuscitation as needed. Adequate pain control generally necessitates judicious narcotic medication and will need to be titrated to effect depending on the patient, location, and extent of the burn. Patients with extensive partial-thickness burns may need a patient controlled analgesia (PCA) to help manage their pain. Cold sterile water irrigation can be used to clean the wound once pain is controlled as cold water may reduce the depth of the burn and improve the cosmetic outcome [15]. Blisters larger than 6 mm are likely to rupture on their own and should be debrided to prevent infection and mechanical pressure on underlying tissue. Evidence suggests blisters less than 6 mm can be left intact [16]. Topical silver sulfadiazine (SSD, Silvadene) has historically been used for its antibiotic properties and to promote healing; however, a recent Cochrane review suggests higher infection rates and longer hospital stays with SSD when compared with newer synthetic or biosynthetic burn dressings or skin substitutes, of which there are numerous commercial brands [17]. SSD also requires more frequent painful dressing changes when compared to the newer occlusive dressings and as such is typically used as a last resort.

Full-Thickness Burn

Management of full-thickness burns should not be left solely to the family physician except in rare

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circumstances. These patients are best served by seeing a burn specialist and surgeon early in their course for possible debridement with skin grafting. The family physician will need to facilitate a consult to a burn specialist, establish pain management, document the involved area, initiate fluid resuscitation, prevent infection, and monitor for complications. Patients with large full-thickness burns will need continuous reassessment for shock and compartment syndrome while awaiting transfer to a burn center. Systemic antibiotics have not been shown to prevent infection or mortality and are currently not recommended for prophylaxis [17].

Fluid Resuscitation

Burn patients may require fluid resuscitation depending on the extent of their burns. The Parkland and modified Brooke formulas have historically been used; however, studies have indicated that these formulas lead to over-resuscitation and potentially increase morbidity and mortality [18]. More recently, burn centers and the US Army has started using the "rule of 10" to simplify fluid resuscitation. In this validated formula, the %TBSA is rounded to the nearest 10 and multiplied by 10 to give the initial fluid rate in milliliters per hour (ml/h) for an adult weighing between 40 and 80 kg. An additional 100 ml/h of fluids is recommended for every 10 kg over 80 kg the patient weighs [19]. The best marker of adequate fluid resuscitation is urine output with a goal of at least 0.5 ml/kg/h. Over-resuscitation can lead to significant peripheral edema that can complicate skin grafts, cause pulmonary edema, or cause the feared condition of abdominal compartment syndrome.

Prevention

Prevention of burns can be accomplished with education and counseling. Parents should be warned of a child's increased risk of burns and encouraged to use extra precaution when cooking or handling hot liquids around infants and children. Adolescent-age children should be supervised when around fireworks, gasoline, or open fires. Alcohol and drug use should be avoided when near open fires. Proper precautions should always be practiced when near explosive gases such as propane. Smoke detectors should be checked at least annually [15].

Swallowed Foreign Body

General Principles

Definition/Background

Ingestions of foreign bodies are most common in children who have an affinity for putting objects in their mouths. Adults with foreign body ingestion are usually food related, psychiatric, or a self-inflicted injury. Most ingested foreign bodies pass spontaneously; however, an estimated 10–20% of ingested foreign bodies require endoscopic procedure and less than 1% requires an operation [20]. Swallowed foreign bodies can be classified as blunt (coin, battery), sharp (needles, bones, razors), food bolus, or caustic/toxic (battery).

Ingestion of a foreign body may cause pain and possible airway involvement, and in severe cases, it can involve esophageal or gastrointestinal perforation. Evidence suggests that up to 50% of cases are asymptomatic in children and as such require a high level of suspicion [21]. Small batteries can cause perforation of the intestinal lumen due to their corrosive effect on mucous membranes. Magnets, especially rare-earth magnets known as BuckyBalls, can present a problem when more than one is swallowed. These strong magnets can reposition bowel and cause pressure necrosis through up to six layers of bowel wall, often requiring laparotomy to remove the magnets and repair damaged bowel [22].

Approach to the Patient

Diagnosis

History

Foreign body ingestion should be ruled out when evaluating a child with sudden onset of vomiting,

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stridor, or wheezing. Keeping in mind that half of these cases can be asymptomatic, a high level of suspicion should be maintained when evaluating children with decreased appetite; vague abdominal, chest, or throat pain; failure to thrive; drooling; cough; irritability; or gagging [21]. Caretakers should be questioned about the possibility of foreign body ingestion, being sure to ask about batteries, coins, or magnets that a child may have had access to. Adults with foreign body ingestions can generally provide a reliable history of what and when the ingestion occurred unless they are intoxicated or have psychiatric illness, in which case they should be approached the same as a pediatric patient.

Physical Examination

Examination should include vital signs to evaluate respiratory rate, pulse oximetry, pulse, and temperature. Tachycardia and fever can indicate potential complications of foreign body ingestion such as perforation. The oropharynx should be examined for any visible evidence of the foreign body. A standard physical exam of the neck, heart, lungs, and abdomen should be completed.

Laboratory and Imaging

Radiographs including anterior-posterior and lateral views of the neck, chest, and abdomen are the initial studies of choice to evaluate for radiopaque foreign bodies as well as evaluate for free air in the setting of perforation. CT scanning may be more sensitive for foreign bodies with one study reporting 100% sensitivity for foreign bodies including radiolucent fish bones [23]. Contrast studies such as a barium swallow are not recommended due to the risk of perforation, the risk of aspiration, and the potential to make endoscopy more challenging [24]. Unfortunately, not all foreign bodies are radiopaque, and if the level of suspicion is high enough with persistent symptoms, endoscopy should be undertaken for both diagnosis and treatment.

Treatment

The treatment of ingested foreign bodies depends on the location of the object, the type of object, and the presence of any complications. Observation is a reasonable option in some cases if the patient is asymptomatic and the object has passed the esophagus. If the object is still in the oropharynx, an attempt to remove it with Magill forceps should be done. Recommendations for endoscopic retrieval of the foreign body are outlined in Table 2. In rural or austere settings, providers have successfully removed esophageal foreign bodies, typically coins or blunt objects, by passing a Foley catheter down the esophagus, filling the bulb distal to the object, and pulling the object out in a retrograde direction. This does carry a risk of airway obstruction and should only be used as a last resort. Similarly, a bougie can be used to push a blunt object from the esophagus into the stomach as 90% of objects that make it to the stomach pass spontaneously [21]. Both of these techniques are contraindicated if the foreign body is sharp. If the object is beyond the reach of endoscopy, it should be followed with serial radiographs daily for sharp objects and weekly for blunt objects [21]. Symptoms of perforation such as fever, tachycardia, distended abdomen, free air on radiography, and/or peritoneal signs should prompt surgical consult. Patients presenting following ingestion of illicit drugs packaged into balloons

Table 2 Endoscopic management of ingested foreign bodies (Source: adapted from Ikenberry et al. [24])

Endoscopic management of ingested foreign bodies		
Emergent	Urgent	Nonurgent
Airway involvement	Blunt objects in the esophagus	Coin in the esophagus >24 h
Esophageal obstruction	Incomplete esophageal obstruction	Objects in the stomach >2.5 cm
Esophageal battery or sharp object	Sharp foreign bodies in the stomach or duodenum	Batteries in the stomach >48 h
	Magnets	

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should be observed as inpatients for obstruction as endoscopic removal is contraindicated for fear of rupturing the package and causing an overdose [20].

Prevention

Parents should be educated at well-child visits to keep small items, batteries, magnets, and coins out of the reach of small children.

Fishhook Removal

General Principles

Fishhooks are intended to catch fish; however, many fishermen/women have been accidentally snagged. This may present in an urgent care setting, or a family physician may be called upon to help at the scene of the injury. The hand is the most commonly affected area followed by the head and face [25]. The difficulty in removing a fishhook is due to the barb that is designed to prevent a fish from getting off the hook once it has been set (Fig. 3). When dealing with imbedded fishhooks, there are five proposed techniques for removal, each with their own risks [26]. Hooks imbedded in the eye require urgent consultation to specialized care and should not be removed by untrained individuals. To date, there have been no head-to-head comparisons between the methods described below.

Common to all methods for fishhook removal is the need for aseptic technique and local anesthesia. Infiltration of lidocaine 1% using a 25 gauge needle around the involved area or in a digital block works well to achieve adequate anesthesia. Chlorhexidine or iodine-based scrubs around the entry point are reasonable choices to clean the area prior to the procedure [27]. In austere environments, normal saline or clean tap water irrigation would be acceptable methods for cleaning and prepping the area. After the hook is removed, the puncture wound should be washed thoroughly.

Treatment

The patient's tetanus immunity status needs to be determined and appropriate prophylaxis administered after removal of the hook. Antibiotics with activity against *Aeromonas hydrophila*, such as an oral fluoroquinolone, can be considered prophylactically for contaminated deep puncture wounds [25, 26].

Removal

Retrograde pull. Barbless hooks exist and can simply be removed by pulling straight out of the skin along the path of entry (Fig. 4). Additionally, hooks that are not fully set or that are very superficial can be removed using this technique. Use



Fig. 3 Common fishhooks. The hook on the left is a treble hook. Note the barbs at the head of each hook. The far-right hook has a very small barb that might allow for retrograde pull removal

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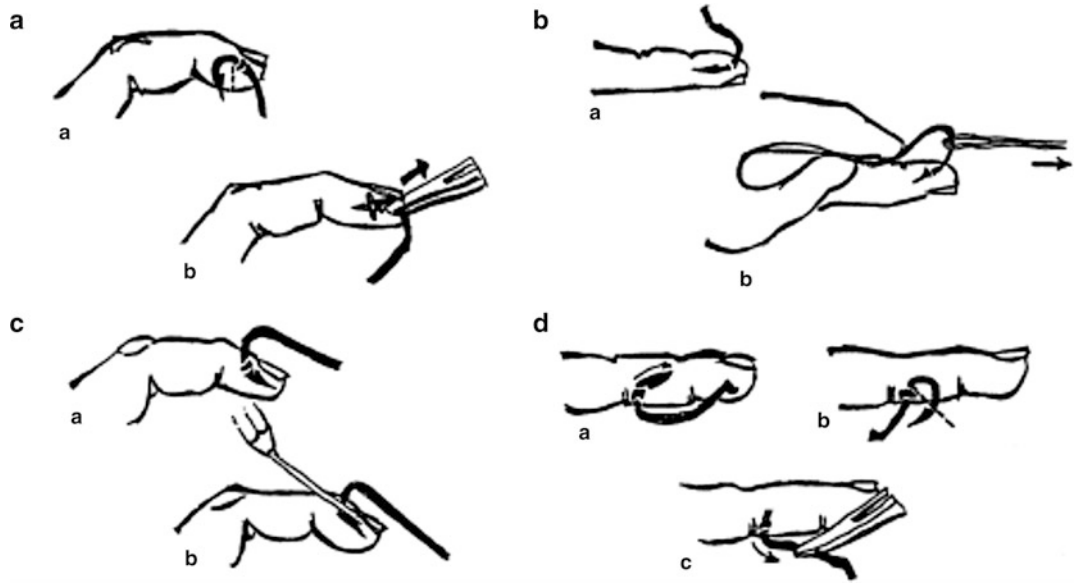


Fig. 4 Fishhook removal. (**a**) Simple retrograde pull. (**b**) String-yank technique. (**c**) Needle-cover technique. (**d**) Push and cut technique (Source: David et al. [28]. With kind permission of Springer Science and Business Media)

hemostats or needle-nose pliers to ensure positive control of the fishhook while performing this technique. This method can cause local tissue damage and is not suitable for deeply embedded hooks, hooks that are near neurovascular structures, or hooks with large or multiple barbs.

Hook depression and string pull. This technique attempts to disengage the barb by depressing the hook while simultaneously pulling the hook out using a string. The string needs to be strong enough that it will not break, and it works best if the string is wrapped around the hook at least once if not more depending on the diameter of the string. High weighted fishing line, umbilical tape, iodoform packing tape, and shoe string are examples of string that can be used. Ensure a solid grip on the string with one hand, and with the other hand, depress the eye of the hook down toward the skin. Then give a firm pull to the string in a retrograde direction to pull the hook out the way it entered the skin. This technique can cause some local tissue damage as it pulls the hook out and as such is best suited for superficial hooks that are not near nerves or vessels. Additionally, this method requires two hands and cannot be performed by an individual on themselves. Ensure eye protection is worn while attempting this method.

Needle cover. An 18 gauge needle can be utilized to cover the barb of a hook and allow it to be removed in a retrograde manner along the path of entry (Fig. 5). The needle is inserted into the skin at the site where the hook has entered and blindly follows the hook to its barb. Once the barb has been covered by the lumen of the needle, it allows the hook to be withdrawn. This technique is not ideal for deeply set hooks or hooks with large barbs.

Advance and cut. The advance and cut technique is felt to have the best initial success rate and is best suited for deeply set hooks. The downside is the additional trauma it causes. The hook is controlled with pliers or a hemostat and advanced in a direction that brings the point and barb of the hook through the skin at a different location. Once through the skin, the barb may be broken off with the pliers or the hook can be cut proximal to the barb (Fig. 6). Simply back the hook out the path of entry after removing the barb. A variation of this method involving an incision and direct visualization of the advancing hook has been used for a deep hook near the ulnar nerve and muscles of the hand [25]. This and the incision and removal technique described below are the only techniques likely to work when dealing with a hook that has

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Fig. 5 Needle-cover technique. Note the hook is grasped with pliers and the needle enters at same location as the hook. This is an 18 gauge needle. No pigs were harmed in the making of this image



Fig. 6 Advance and cut technique. Note the barb has been advanced through the skin and the hook will be cut proximally to the barb. No pigs were harmed in the making of this image

multiple barbs along its shaft. In this method, the hook is advanced and the end opposite the barb (where the eyelet to attach the fishing line to is located) is cut close to the skin, and the hook is advanced all the way through the skin without attempting to reverse the direction of the hook. Take note that eye protection should be worn while cutting the hook, and don't underestimate the force required to cut a hook. Powerful pliers are needed for cutting even small fishhooks.

Incision and removal. Another acceptable method for removal is to use a scalpel to make a small incision over the hook and simply remove once exposed. This method typically leaves a larger wound but can be irrigated and dressed with good healing. This method can be considered the last option if other methods fail.

Prevention

Eye protection, long sleeve clothing, and gloves may provide some protection from fishhook injuries.

Disclaimer The views expressed are those of the author and do not reflect the official policy of the Department of the Army, the Department of Defense, or the US government.

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Part XII

Care of the Athlete

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Medical Problems of the Athlete

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Introduction

Family medicine encompasses a wide range of disease processes that can benefit from regular physical activity. In addition, the specialty serves a population that can span from elite athletes to a sedentary desk worker and from a geriatric speed walker to a peewee football player. It is important to understand how the diagnosis, management, and approach to these patients and their varying disease processes differ in the setting of exercise. This chapter examines medical conditions such as asthma, hypertension, diabetes, anemia, and various skin diseases in the setting of athletes, as well as the unique features of physical activity in several special populations.

Physical Activity Guidelines

Regular exercise has been shown to decrease the risk and improve control of many chronic diseases. Data over the last several decades clearly support the benefit of regular physical activity on improving obesity, cardiovascular disease, metabolic syndrome, bone health, and mental health. The United States Department of Health and Human Services (HHS) recently reviewed national and international data relating to physical activity and health. Their 2018 update continues to recommend the average adult engage in at least 150 min a week of moderate-intensity (brisk walking) or 75 min a week of vigorous intensity (light jogging) exercise [1]. Increased health benefits are gained when engaging in moderate-intensity physical activity for at least 300 min a week. Muscle strengthening of all major muscle groups two times per week is also encouraged [1].

Approach to the Athlete as a Patient

Exercise Physiology

Physical activity puts stress on the body that is important to understand when approaching patients that are athletes. There are two forms of exercise, anaerobic and aerobic. Anaerobic consists of short sprints and resistance training, in order to promote strength, speed, and power. Aerobic involves longer endurance training and requires more oxygen to maintain. Both forms are dependent on the ability to deliver oxygen effectively, and there are several adaptations to the cardiac, respiratory, and hematological systems that occur to optimize performance. In addition, regular exercise results in physiological adaptations of the heart that are important to understand when managing athletes.

Physical activity increases the body's metabolic demand for oxygen and energy sources. In order to meet these demands, the heart must increase cardiac output with an increase in heart rate and stroke volume. Systolic blood pressure increases with increased work, and blood is shunted from splenic and GI organs to the muscular system. In order to meet the almost exclusively aerobic metabolism of the heart, increased coronary artery perfusion is necessary and is accomplished from an increase in perfusion pressure and coronary vasodilation. Exercise also stimulates the sympathetic nervous system which results in a release of catecholamines to further increase coronary perfusion.

With regular activity, these changes that occur acutely during exercise will result in long-term changes of the cardiovascular system. Specific changes in the heart are referred to as the "athlete's heart." These changes consist of increased left

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ventricular mass, increased left ventricular wall thickness, and increase in left ventricular end-diastolic volume [2, 3]. Echocardiogram-based studies have also shown an increase of size in the interseptal and posterior walls of the heart as well as larger ventricular diameter [2, 3]. For reasons that are not completely understood, well-trained athletes have reduced sympathetic activity and increased parasympathetic activity resulting in baseline bradycardia. Cumulatively, these changes ultimately allow for higher stroke volumes at a lower heartrate [2].

The need for rapid exchange of oxygen and carbon dioxide during exercise results in an increase in tidal volume followed by increased respiratory rate to improve ventilation. Over time with regular physical activity, the respiratory system can adapt with an increase in maximal voluntary ventilation. Other minor changes can occur over time, but adaptations here are less than in the cardiovascular system, and it is thought that the limitations in exercise secondary to a healthy respiratory system are small [2, 3].

Oxygen delivery can also be affected by the hematologic system and the body's ability to carry and deliver oxygen to the working tissues. Red blood cells (RBC) contribute to oxygen delivery via three important mechanisms. (1) They are a source of nitric oxide which causes vasodilation and increases blood flow to tissue. (2) As the oxygen-carrying cell of the body, an increase in the number of RBC will enhance oxygen delivery. (3) The viscosity of blood, which is partially affected by RBC membranes and their deformability, affects the velocity of blood through the microvasculature. It is thought that the sequelae of exercise-dehydration, lactate production, and hypoxia-impair blood viscosity during actual episodes of exercise, ultimately results in a decrease of whole blood viscosity in the resting athlete and thus supports tissue oxygenation [4]. Anemia and sickle cell are examples of conditions that will be addressed where this oxygen delivery can be affected.

In addition to cardiac and respiratory changes, understanding the metabolic demands on a patient is important, especially when managing disease processes such as diabetes that can affect the ability to manage fuel. The main fuel source during exercise is lipid and carbohydrate breakdown from adenosine triphosphate (ATP) and glucose within the muscle. Because of this, there is an insulin-independent uptake and utilization of glucose during exercise, which can help improve overall glycemic control. Under the control of glucagon, epinephrine, and cortisol, fuel utilization will eventually shift to plasma-free fatty acids and blood glucose outside the muscle. In diabetic patients, this metabolic process can be affected due to their inability to properly regulate glucose levels.

Overtraining Syndrome

Overtraining syndrome is a diagnosis of exclusion that presents as unexplained underperformance in an athlete. It is thought to result from increased training loads without adequate recovery. The training load is affected by fatigue (both physical and mental) and recovery, including sleep, nutrition, and physical rest [5]. The exact pathogenesis of overtraining syndrome is unclear; however, there are multiple theories with alterations to the central nervous system seeming to be the leading theory, in particular, a disturbance in the hypothalamic-pituitary-axis [6].

Symptoms can be vague and broad, making a diagnosis difficult. In an attempt to simplify, symptoms can be grouped into parasympathetic (fatigue, depression, anhedonia), sympathetic (insomnia, irritability, hypertension), and other (anorexia, anxiety, ineffective sleep). Parasympathetic symptoms tend to be more common in aerobic sports, while sympathetic symptoms are more frequently seen in anaerobic sports [6].

The wide differential in symptoms requires a thorough history to include focusing on nutrition, rest, hydration, medications, mood, and exercise regimen history. When approaching diagnosis, it is important to rule out organic disease processes with objective workup being guided by specifics of the history and can include but is not limited to CBC, CMP, iron studies, CK, and thyroid studies.

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An important component of diagnosis seems to be mood complaints. Although subjective, mood symptoms can be easily and inexpensively obtained and tracked throughout an athletic season or a career.

Treatment focuses on controlling organic disease processes and modifying training plans to allow for appropriate recovery. If mood symptoms are a major component of the athlete's presentation, the addition of a sports psychologist or counselor would be appropriate. Treatment of mood symptoms with SSRIs could be considered; however, athletes should be informed of the potential for possible decreased performance as a side effect of the medication. As always, a risk/benefit discussion should occur with the patient [7].

Prevention is preferred and can be achieved through education and screening [8]. Athletes should be evaluated at critical points during their training, in particular during increases in training load or personal stressors. Although some screening tools have been evaluated, at this time there is not one specific tool that is recommended [9].

Chronic Disease Medical Problems

Asthma

This common medical condition affects an estimated 7.5% of the American population [10]. Symptoms including wheezing, shortness of breath, and cough are a consequence of airway hypersensitivity to various triggers resulting in bronchial spasm and inflammation. When exercise has been identified as a trigger for chronic asthmatics, it is often referred to as exercise-induced asthma (EIA). Without a diagnosis of underlying asthma, transient airway hyperresponsiveness is more appropriately classified as exercise-induced bronchospasm (EIB). The mainstay of therapy includes inhaled beta-agonist, inhaled steroids, and mast cell stabilizers. Primary care providers should be aware of which sports are associated with higher prevalence of asthma and asthma-like symptoms, identify triggers for athletes, furnish an asthma action plan (AAP), and provide rescue inhalers for all asthmatics for practices and games [11].

There are a few theories on the pathophysiology of EIB, most of which relate to the exchange of temperature and water that occurs during exercise at the bronchial epithelial level. These changes trigger an increase in cell inflammatory mediators. Additionally, exercise triggers bronchoconstriction in normal, healthy patient. Athletes with EIB have been shown to have increased levels of nitric oxide and expression of mast cell genes leading to further bronchoconstriction [4].

Breathlessness, cough, wheeze, chest tightness, and excessive mucus production within the first 5–15 min of exercise with resolution 1 h following cessation of activity are consistent with EIB; however, symptoms cannot solely be relied upon for definitive diagnosis. Pulmonary testing and clinical examination are necessary for definitive diagnosis. Spirometry is an option to assess these patients, but athletes possess a few inherent characteristics that can make result interpretation difficult. Notably, forced expiratory volume (FEV) may be increased above the normal range in conditioned athletes. Additionally, when exercise is truly the trigger, simple spirometry is not enough to induce bronchoconstriction. Patients may require additional bronco-provocation testing to elicit airway restriction occurring secondary to exercise.

To diagnose EIB, athletes need to have a $\geq$10% decline in their FEV1 values measured pre- and post-exercise (known as exercise challenge test). Methacholine challenge testing is often used in athletes exhibiting EIB symptoms with equivocal exercise challenge testing. Patients with EIB will require lower amounts of methacholine before showing an impact in FEV1. The eucapnic voluntary hyperventilation test is the gold standard set by the International Olympic Committee but is not often used in clinical practice [11].

Various environmental factors including location of training, ambient temperature, humidity, and air quality contribute greatly to the onset and perpetuation of bronchoconstriction in the athlete. Two sports disproportionally affected include swimming and cold weather athletes. Thirty percent of athletes in winter sports such as figure skating and skiing are thought to have EIB

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secondary to the inhalation of cold, dry air [4]. Swimmers have exhibited incidence of EIB six times greater than nonathletes and spring/summertime athletes, likely as a result of the chlorine exposure [12].

Patients with allergen-induced asthma suffer compounded risks in periods of high pollen count during seasonal and perennial pollination. Importantly, up to 40% of patients suffering from allergic rhinitis will present similar upper respiratory symptoms to asthmatics during exercising, while being asymptomatic at rest [13].

Management of EIB/EIA symptoms begins with prevention when possible. Correctly identifying symptoms of allergic rhinitis and treating with a combination of intranasal corticosteroids and antihistamines reduces the concomitant effect in chronic asthmatics. For winter athletes, breathing through a scarf can help. Education on proper warm-up including 15-min moderate warm-up period followed by a 15-min rest period which can induce a refractory period.

Pharmacologic intervention should be considered with failure of conservative measures. First-line therapy is use of a short-acting beta-agonist 15 min prior to exercise. Daily inhaled corticosteroids (ICS), leukotriene antagonists, or mast-cell stabilizing agents are second line. The Global Initiative for Asthma (GINA) recently released a major change in recommendations for mild asthma. In this, monotherapy with short-acting bronchodilators (SABA) is no longer recommended as initial treatment. Instead, GINA recommends that all adults and adolescents with any form of asthma receive ICS-containing controller treatment for maintenance and exacerbation therapy [14]. Given the significant paradigm shift with these new recommendations, further research is needed to assess the efficacy of this approach in patients with mild asthma and EIB/EIA.

Cardiac

Hypertrophic cardiomyopathy (HCM) represents the most common genetic cardiovascular disorder with an estimated prevalence of 1:500 of the general population. Common symptoms include shortness of breath (particularly with exertion), chest pain, palpitations, orthostasis, presyncope, and syncope. Many patients remain asymptomatic with a benign natural history; unfortunately, sudden cardiac arrest/death can be the first manifestation in otherwise asymptomatic young people. HCM has been positively identified in well over a third of cases (36%) of SCD in athletes under the age of 30 and cited as a possible cause in another 8%. Symptoms vary widely between individuals, even those in the same family. Differentiating between HCM and physiologic nonpathological left ventricular (LV) hypertrophy associated with extensive training ("athlete's heart") can be difficult. Definitive diagnosis has important implications as HCM will likely lead to disqualification from competition to minimize risk.

Identification of this disorder falls to the family medicine physician using specific criteria and disease-specific questions noted during the patient reported history and pre-participation physical exam. Recent American Heart Association/American Cardiology Association recommendations on pre-participation cardiovascular screening endorse a strategy of a focused medical history and physical examination [15]. This approach relies on the primary care provider to perform adequate, standardized exams that are of low-cost to the patient; *The Pre-Participation Physical Evaluation Monograph 5th Edition* is a wonderful resource to assist primary care providers in this endeavor [16].

Major risk factors for HCM include prior cardiac arrest, unexplained syncope, a family history of SCD, left ventricular wall thickness >30 mm, an abnormal BP response to exercise, and history of non-sustained spontaneous ventricular tachycardia [17]. Some examples of disease-specific questions are:

1. Has anyone in your family died suddenly for unexplained reasons before age 50?
2. Have you ever experienced chest pressure or pain while exercising?
3. Have you ever been diagnosed with a heart murmur?
4. Have you ever had cardiac imaging done?
5. Have you ever passed out or nearly passed out during or after exercise?

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The physical exam for HCM has been an insensitive screening tool for sole identification. This is in part due to most patients with HCM presenting with a nonobstructive disease and unremarkable cardiac exam [17]. Patients presenting with left ventricular outflow tract obstruction most commonly exhibit a late-systolic ejection murmur best appreciated at the left sternal border. This murmur commonly radiates to the aortic and mitral posts, typically heard best when the patient stands or performs the Valsalva maneuver which decreases preload to the heart.

If HCM is suspected based on patient history, physical exam, or a combination of the two, referral to a cardiologist is indicated. An in-office EKG should be considered for athletes whom you suspect to have cardiac dysfunction. Advanced imaging of cardiac function by echocardiogram and/or cardiac MRI is the gold standard for diagnosis of HCM, which is exhibited by asymmetric LV wall hypertrophy (wall thickness $\geq$13 mm) without chamber dilation. Mild concentric LV hypertrophy (13–14 mm) may be present in healthy individuals who exercise strenuously and indicative for "athlete's heart" [18]. Anterior septum thickening and abnormal systolic motion of the mitral valve may be evident as well. Following identification, disease management is tailored around disease symptoms, risk, and complications becoming largely empiric as no large-scale studies for the medical management of HCM exist to date.

Diabetes

Diabetes is a common disease that affects roughly 15% of the adult population in America [19]. It has been well established that regular physical activity can help prevent the development of diabetes as well as serve to improve glycemic control. Regular physical activity reduces the risk of cardiac death of diabetic patients by 30–40% [1]. In addition, an active lifestyle assists in reducing blood pressure, body weight, cholesterol, and A1c in diabetic patients independent of diet. HHS Guidelines recommend at least 150–300 min a week of moderate-intensity, or 75–150 min of vigorous activity per week. Preferably, aerobic activity should be spread throughout the week. The greater amount of aerobic activity, the greater the health effects seen [1]. With the increased risk for coronary artery disease in the diabetic population, it is important to consider cardiac screening in these patients; however, the benefits of regular exercise far outweigh the cardiac risks.

In type 1 diabetics, there are three considerations when participating in athletics. First, exercise lowers blood glucose independent of insulin, which puts the patient at risk for hypoglycemic events. Second, on the other hand, exercise stimulates the sympathetic nervous system and release of stress hormones such as cortisol and epinephrine and can result in hyperglycemia. This, coupled with the possibility of low insulin levels prior to starting exercise, puts the type 1 diabetes at increased risk of ketogenesis. The final concern for these athletes is delayed hypoglycemia. Tissue insulin sensitivity is increased for 7–11 h post exercise. If carbohydrates are not replaced, the athlete is at risk for hypoglycemic events for up to 12 h after finishing exercise [20, 21].

Several recommendations can be made to type 1 diabetes to avoid these complications. Adjustments to carbohydrate intake rather than insulin dosing are associated with fewer exercise-related complications [20, 21]. Athletes should check their blood sugar prior to exercise, and if less than 150 mg/dL, they should supplement with a high-carbohydrate snack [21]. Due to risk of ketogenesis, vigorous physical activity should be avoided in patients with hyperglycemia $\geq$250 mg/dL [22]. For endurance athletes, training sessions longer than 1 h should consider carbohydrate supplementation [20, 21]. All athletes should have a post-exercise snack in order to combat the delayed hypoglycemia risk as well as frequent blood sugar checks every few hours in that post exercise period [20].

The insulin pump is widely accepted tool for managing type 1 diabetes. In athletes well versed in managing their pump, this is a good way to minimize glycemic fluctuation. It can also be titrated to allow for regular exercise sessions.

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Hematological Disease

Anemias

As discussed above, blood and its ability to transport oxygen are an important part of an athlete's performance ability. A phenomenon known as "sports anemia" occurs most commonly in endurance athletes. Repetitive long workouts cause hemoconcentration from dehydration which leads to an overshoot of plasma expansion post-exercise and Hgb levels up to 1.5 g/dL below normal [23]. Sports anemia is exceedingly uncommon in non-endurance athletes. Diagnosis can be tested by stopping workouts and assessing Hgb values approximately several days later. The athlete's Hgb should normalize within 5 days [23] if present. As this is an physiologic, adaptive response, no treatment course needs to be pursued.

Much like the general population, iron deficiency is the most common form of anemia seen in athletes. The rate of occurrence is no different than the general population. Iron deficiency anemia (IDA) can occur in up to 20% of menstruating females, 6% of postmenopausal women, and 4% of male athletes, respectively [23]. Etiologies for IDA include GI bleeding, NSAID use, and menstruation in females. Sport-specific causes such as hematuria, foot-strike destruction, and iron loss from sweating have been described in the sports literature, but should be low on the differential and diagnoses of exclusion [23]. Iron deficiency anemia should be worked up and treated similarly to iron deficiency anemia in the general population.

Recent studies have examined Iron Deficiency Non-Anemia (IDNA) where ferritin levels are low but true anemia is not present. Experimental treatments with both oral and IV iron supplementation have been examined for their effects on fatigue and potential benefits for VO2 Max. The evidence for these practices is currently inconclusive [24]. Given the controversial nature of this therapy, athletes thought to have IDNA should be referred to a sports specialist for evaluation and management.

Macrocytic and hemolytic anemias in the athlete have similar etiologies and treatment to that of the general population. The phenomenon of foot-strike anemia (also thought to be a cause of microcytic anemia), mentioned above, is a rare and often clinically insignificant disorder that occurs in endurance athletes from repetitive heel strike, muscle use, or cardiac valve turbulence and rarely requires treatment [25].

Hemoglobinopathies

Thalassemia results from the deletion or mutation of genes responsible for the alpha and beta chains that make up hemoglobin. Anywhere from one to four of the chains can be affected and range from asymptomatic to death in utero. Sickle cell trait (SCT) occurs when an individual is heterozygous for sickle hemoglobin (HgbAS). Under normal physiological conditions, SCT is typically benign and easily controlled; however, excessive heat, high-altitude, and intense training can result in sickling of RBCs in athletes within minutes. The exact mechanism causing the sickling is not completely understood, but it causes an increased risks of medical complications such as splenic infarction, hematuria, exertional rhabdomyolysis, and sudden death in SCT athletes. In studies of military personnel, the risk of exercise-related death in warfighters with SCT is estimated to be approximately 40 times higher than those without. Although absolute risk remains small, SCT is the leading cause of death in young African Americans in military basic training and civilian organized sports [26].

In all athletes, SCT should be a significant topic for counseling during pre-participation physical examinations. Best practice guidelines produced by the National Collegiate Athletic Association (NCAA) states that all college athletes in the United States are required to know and report their sickle cell status or sign a waiver after education of potential risks related to SCT [27]. In athletes with known SCT, appropriate precautions should be taken with regards to training and competing. The athlete should be conscientious of staying well hydrated and tapering workouts to not overexert themselves, especially in hot and high-altitude conditions.

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Skin

Tinea Corporis Gladiatorum

Tinea corporis gladiatorum (TC) is a fungal rash caused by *Trichophyton tonsurans* most often seen in contact sports, especially wrestling [28]. It is transmitted by skin to surface contact and has been thought to be transmitted by asymptomatic tinea capitis. TC presents as well-defined, erythematous, scaling plaques most commonly on the head, neck, and upper extremities. It often is not as ring-shaped as typical tinea corporis. Diagnosis can be done via a KOH prep and presence of hyphae but is more often simply clinical [29].

Treatment can be either topical or oral. Topical application of clotrimazole twice daily or oral fluconazole 200 mg weekly is recommended treatment. Athletes can return to practice and competition after a minimum of 72 h of treatment. The most important aspect of treatment is prevention. Discouragement of equipment sharing among the athletes and encouragement of frequent cleaning of personal equipment are effective prevention strategies.

Herpes Gladiatorum

Herpes gladiatorum is a common rash in athletes with close physical contact such as wrestler and rugby players. This non-genital herpes simplex virus infection is commonly seen on the torso, though can present wherever skin to skin contact occurs. Presentations typically consist of erythematous papular and vesicular eruptions. Although this diagnosis is usually made clinically, definitive diagnosis can be made via viral culture or PCR testing from open ulcers. Given its limited sensitivity and specificity, the Tzanck test has fallen out of failure.

Treatment of herpes gladiatorum is initially aimed at prevention of spread. Athletic participants in wrestling and rugby should be screened for active, open lesions with prompt removal of affected athletes from participation if identified. Treatment consists of antiviral therapy, such as acyclovir or valacyclovir. For primary cases, the athlete needs to be treated for a minimum of 10 days before allowed to return to competition. If systemic signs or symptoms present during the initial outbreak, removal from competition should be extended to 2 weeks. For subsequent outbreaks, 5 days of treatment, all lesions being dried and scabbed over, and no new lesions in the past 48 h are requirements for return to participation. Antiviral prophylaxis has become a common practice in higher levels of wrestling competition.

Tinea Pedis

Another common fungal infection among all athletes is tinea pedis caused by *T. rubrum*, *T. mentagrophytes*, and *T. interdigitalis*. Walking barefoot on communal floors, wearing occlusive footwear, sweating excessively, and poor circulation all predispose athletes to this infection. Like tinea corporis, the diagnosis can be made clinically. KOH prep may be needed as tinea pedis can present similarly to other dermatological disorders such as contact dermatitis, foot eczema, psoriasis, or juvenile plantar dermatosis [29]. Over-the-counter antifungals are a reasonable first line for treatment followed by prescription topical antifungals. These should be applied twice daily for 2–4 weeks. If the rash is still resistant, then oral agents such as terbinafine (250 mg daily for 2–6 weeks) or itraconazole (200 mg daily for 2–12 weeks) should be tried.

Staphylococcus and *Streptococcus*

Staphylococcus and *Streptococcus* can cause two common rashes among athletes: impetigo and folliculitis. These are most common in contact sports such as rugby, football, and wrestlers. Impetigo is due to localized, superficial infections causing well-defined, erythematous, yellow, crusted plaques. Impetigo can be spread through skin to skin contact through breaks in the skin or even atraumatic skin [30]. Folliculitis occurs when these bacteria infect the athlete's follicles. The hair follicles become erythematous and can have

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pustular drainage. The rash tends to be itchy and if deeper also painful.

Topical Mupirocin can be used, but with extensive disease, treatment with penicillin or cephalosporin is recommended for a week. If MRSA infection is suspected, treatment should be considered with doxycycline or sulfamethoxazole/trimethoprim [30]. The athlete should be removed from participation for a minimum of 72 h of treatment. In team sports with multiple infections, it is important to consider the possibility of nasal carrying of *Staphylococcus*. Mupirocin ointment applied to both nares twice daily for 1 week should clear *Staphylococcus* carriage for about 6 months.

Nail Dystrophies

Trauma and pressure to the nail plate and periungual area can result in changes that often look similar to onychomycosis. Runners develop jogger's toe from repetitive thrusting of the toe into the shoe that results in a subungual hematoma. The toenail can become thickened, ridged, and discolored from this repetitive trauma. Sports with quick stops and starts such as racquet sports and basketball can result in similar destruction of the nail bed. There is typically no need for treatment, and the nail can be watched for changes that would point toward an alternative diagnosis such as fungal infection or melanoma. Occasionally, the pain from these nail changes will inhibit the athlete's ability to effectively participate. In these instances, evacuation of subungual hematoma by drilling a hole through the nail bed or complete nail removal to address nail bed changes are reasonable treatment options [30]. If pain is severe, one must further consider whether imaging is needed to evaluate for underlying fracture [30].

Talon Noir/Mogul's Palm

Talon noir and Mogul's palm are black macules that result from intraepidermal bleeding as a result of shearing forces. Talon noir occurs on the soles and is most commonly seen in basketball players [31]. Mogul's palm occurs on the hands of skiers from repetitive pole planting. These lesions can be confused with melanoma, and if concern exists, a biopsy should be done. Otherwise, paring down the lesion with a surgical blade can remove the old hemorrhage [30]. If desired, patients prone to these lesions can wear additional padding to aid in prevention [30].

Special Populations

For a family physician, the patient population ranges across all age groups, genders, and demographics. As such, it is important to highlight some of the specific considerations for athletes in these groups.

Women

There are gender-specific benefits to exercise that the family physician should know. Weight-bearing activity can increase bone mineral density and decrease the risks of fracture in postmenopausal women [32]. Studies have shown regular exercise to decrease prolactin and progesterone levels resulting in decreased fatigue, enhanced concentration, and improved premenstrual symptoms of low back pain, pelvic pain, anxiety, and depression [33, 34].

As female participation in sports has increased, a set of health problems that is increasingly prevalent in, but not exclusive to female athletes, has emerged. In 1992 the American College of Sports Medicine first described the female athlete triad as disordered eating, amenorrhea, and osteoporosis. This definition was updated in 2007 to include dysfunction related to energy availability, menstrual function, and bone mineral density. Then in 2014 and most recently in 2018, this topic was expanded further by the International Olympic Committee to be described as relative energy deficiency in sport, or RED-S [35]. RED-S refers to "impaired physiological functioning caused by relative energy deficiency and includes, but is not limited to, impairments of metabolic rate, menstrual function, bone health, immunity, protein

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synthesis, and cardiovascular health" [35]. The main focus underlying this disorder is a mismatch between an athletes' energy expenditure with activity compared to their intake. Low energy availability can be the result of disordered eating in the form of anorexia or bulimia as well as inadvertent decrease in energy intake or failure to increase caloric intake to match the athlete's training program [36]. This low energy availability coupled with the physical and mental stress of training can lead to menstrual irregularity [36]. Finally, this low energy state results in the decrease in insulin growth factor and hypoestrogen leading to low bone mineral density [36].

In 2018, the IOC advised that all physicians caring for athletes need to be aware of RED-S and its associated complications. Although no ideal screening tool exists for the disorder, physicians must be aware of signs and symptoms associated with RED-S including recent weight loss, recent training increases with fuel mismatch, lack of normal growth or development in adolescents, recurrent bony or soft tissue injuries, illnesses, decreased performance, mood changes, and menstrual dysfunction [35]. Ideally, physicians can help educate patients and coaching staffs regarding nutrition intake and expenditure risks, as well as treat patients suffering from complications of RED-S. Treatment should be multidisciplinary and include a physician, dietitian, and often a mental health professional. The focus of treatment is to improve energy balance through improved intake and controlled output in the athlete's training program [36]. Other treatments can include pharmacological therapies such as SSRIs and hormone replacement, but this should be left to the management of specialists.

Pregnancy is another common area in which questions relating to exercise can arise for the family physician. Exercise in pregnancy provides many benefits to include lower risk of gestational diabetes, enhanced sleep, reduced loss of BMD, reduced physical discomfort, maintenance of appropriate weight, improved mental health, and higher APGAR scores [37, 38]. The American College of Obstetricians and Gynecologists (ACOG) found that that there were no reports of exercise-induced hyperthermia leading to teratogenic affects. ACOG's current recommendations in regard to exercise during pregnancy are as follows [39]:

1. Achieve regular moderate-intensity exercise for at least 20–30 min or more on most days of the week.
2. Avoid exercise requiring the supine position after 12 weeks' gestation due to increased risk of obstruction of venous return.
3. Avoid activities that carry with them a risk of abdominal trauma.
4. Avoid physical activity above 6,000 ft.

In summary, women who were previously healthy prior to pregnancy can continue with their training programs during pregnancy. Women with significant cardiac or respiratory disease or complications with the pregnancy should be monitored carefully during exercise [39].

Elderly

The age definition of "elderly" can vary depending on the sport and required skill set. For sports requiring endurance and flexibility, separate age categories can start as early as 19 years. For those demanding a specific skill set, age categories often start at 50 years. For the general public, geriatric classification starts at age 65 with 65–75 being young old, 75–85 being middle old, and over age 85 being very old [40]. The health benefits of physical activity in reducing cardiovascular events, diabetes, and improving bone health continue through the lifetime, and as such elderly patients should be encouraged to continue to be physically active. It is important however to understand some of the physiologic changes that occur and should be considered when treating elderly athletes.

As a person ages, cardiovascular function declines resulting in a decrease in maximal heart rate, impaired compliance in diastole, incomplete emptying in systole, and reduced inotropic response to sympathetic input [41]. This can affect the elderly's activity tolerance level as well as put them at increased risk for arrhythmias and heart failure. The other major physiologic change in the elderly is sarcopenia – or a decrease in muscle

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mass, strength, and endurance – which can lead to a decline in functional ability and flexibility putting the elderly at an increased risk of injury and falls [32, 41].

Older adults should strive for the same multimodal exercise goals as stated above for all adults, but with special interest placed on balance training. Family physicians should assist their geriatric patients in understanding how their chronic medical conditions affect their ability to participate in regular activity and modify accordingly as their abilities allow. Ultimately, a simple goal of being more active than sedentary throughout the day is an easy one to advocate to your patients [1].

Pediatrics

The CDC estimates that 18% of children 6–11 years old and 21% of adolescents aged 12–19 were obese [42]. It is now a public health concern to encourage children and adolescents to participate in physical activity in a healthy and beneficial way. It is important to be aware of some of the medical considerations for this younger population, as well as the recommendations for appropriate physical activity. Children should participate in at least 60 min of vigorous aerobic activity daily. Resistance training such as tug of war, rope climbing, or push-ups should be incorporated three nonconsecutive days per week. Preschool children's growth and development is enhanced by regular, daily physical activity [1]. The benefits of following these recommendations include healthy body composition, increased development of bone mass, improved self-esteem, and decrease in anxiety and depression [43].

Early sports specialization has become topic of interest in the pediatric population. Early sports specialization is commonly defined as the participation in one sport at the expense of participation in other sports [44]. Over the past 20 years or so, there has been a shift in the focus of youth sports from a recreational, learning environment to one of competition and dedicated training in order to achieve excellence, scholarships, and even future careers as a professional athlete [45]. Research has found that increased sports specialization from a young age may bring with it an increased risk of musculoskeletal injury, especially with regard to chronic overuse injuries. It may be beneficial to encourage athletes to participate in various sports and activities for both development, opportunities, and to decrease injury risk [46].

In order to participate in sports, most states and sports governing bodies require a pre-participation evaluation (PPE) . In the past, PPEs were thought of as a brief evaluation in the office, often by a provider unknown to the athlete, where one could quickly go to check a box to play their desired sport. Recent changes to the PPE guidelines promote a more well child/adolescent visit approach to these encounters [16]. Ideally, the examination should be performed in the patient's medical home by their primary care physician and if able, as part of the routine wellness visit. The visit should go beyond the standard cardiac and musculoskeletal screening but now include evaluations of mental health, risky behavior screening and counseling, and promotion of healthy lifestyle. The pre-participation evaluation may be the only opportunity for a pediatric athlete to visit a doctor's office, and as such, it is an excellent chance to evaluate, teach, and treat this patient population [16].

Hypertension in the pediatric population is defined by a blood pressure that is $\geq$95th percentile for age, gender, and height, or $\geq$130/80 on three separate measurements [16]. Due to risks involved, these athletes should avoid power lifting and body building until successfully treated [16].

Mononucleosis is a common virus in the adolescent population. Athletes should be removed from activity for at least 3 weeks in order to prevent complications from splenomegaly. The restriction involves all activity, not just contact activities. Return to sport/activity is usually gradual as the patient works back into physical fitness.

Transgender

Transgender individuals identify as a different gender than their sex designation assigned at birth [47]. In 2017, the estimated prevalence of transgender individuals in the United States was 390 in 100,000 [48]. Transgender individuals are

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very frequently cared for by the family physician, and as such, it is important for the physician to help with their cares as a transgender athlete. This includes but is not limited to a focus on the athlete's physical and cardiovascular health, endocrine/hormonal treatments, mental health, bone health, and even being aware of surgeries they have had or plan on having in the future.

Sports and competitions are often divided by sex, but as transgender athletes become increasingly prevalent in the sports arena, controversy exists for their participation [16]. Recent policy from the IOC in February of 2019 attempted to establish guidelines for transgender participation [49]. These policies are new and constantly under scrutiny, controversy, and need of further refinement. Transgender athletes have important and difficult considerations to tackle in the sporting arena. Yet promoting these athletes' health and their ability to participate equally in sport and competition should be a priority for the family physician [50].

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Athletic Injuries

55

T. Jason Meredith, Nathan P. Falk, Jordan Rennicke, and Hannah Hornsby

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Introduction

With the continued increase in sports participation, musculoskeletal concerns account for a significant percentage of patient encounters within family medicine. High school athletics alone account for over two million injuries, half a million physician visits, and 30,000 hospitalizations annually [1]. Growing sports specializations within adolescents has led to an increase in overuse injuries. Adults are not immune to athletic injuries. Weekend warriors commonly experience ankle injuries, knee injuries, joint dislocations, and overuse injuries in attempts to stay active. Injuries occur after an insult to bone or soft tissue structures (muscle, ligament, or tendon) producing disruption in the normal anatomy. Acute injuries usually result secondary to trauma. In contrast, chronic injuries occur as the result of overuse, usually with associated biomechanical deficiencies. Lack of appropriate rehabilitation to injuries can lead to increased injury risk in the future. While the majority of sports-related injuries occur to the axial skeleton, concussions are becoming a growing concern within our society. This chapter will discuss both general treatment options and treatment for specific athletic injuries.

General Injury Management

The initial management of sports-related injuries involves decreasing inflammation, addressing pain control, and stabilizing surrounding tissues to prevent additional injury. Inflammation can be reduced with rest, ice, compression, and elevation (RICE). Nonsteroidal anti-inflammatory drugs (NSAIDs) can assist in both reduction of inflammation and pain control. Pain control can also be accomplished with immobilization, acetaminophen, muscle relaxants, or opioids. Opioids should be reserved for patients in severe pain

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after significant injuries such as joint dislocations and fractures that are not responding to the more conservative treatment options outlined above. Imaging of the injured area is usually required. Options include X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Imaging will alert the physician if anatomical alignment needs to be obtained through reduction of the affected joint or bone. After initial management with immobilization, most patients require some form of physical therapy to address underlying muscle flexibility, muscle strength, and biomechanical deficiencies. Physical therapy is important not only to treat deficiencies resulting from the injury but also address biomechanical issues that increase the risk of future injury. Unfortunately, some injuries cannot be managed conservatively, and referral for operative management is required for definitive treatment.

General Fracture Management

A large percentage of nonoperative fractures can be managed by family physicians. Physical examination at the initial visit should assess for neurovascular complications and associated soft tissue injuries; specific anatomic findings and examination findings will be addressed later in this chapter. All fractures need to be visualized in at least two different views on plain films to ensure appropriate anatomical alignment. If clinical suspicion for a fracture is high but plain films are negative, additional imaging with CT or MRI could be warranted. All fractures should be assessed for closed/open status, fracture pattern, displacement, angulation, and rotation in order to provide appropriate care.

The healing of fractures occurs over a several month period. The initial inflammatory phase occurs immediately after injury with recruitment of inflammatory cells in formation of a hematoma. Osteoblastic cells are then recruited and responsible for the initial remodeling of the injury site. Within the first 2–3 weeks, a soft callus is formed signifying the arrival of osteoclastic cells. By weeks 6–8 post injury, a hard callus replaces the soft callus; this signifies clinical union. It is important to remember that this initial callus is weaker than normal bone. Final bone strength and radiographic resolution occur 3–6 months after initial injury. Multiple factors including smoking, diabetes, and chronic oral steroid usage are can inhibit bone healing. NSAID usage, especially during the first 2–3 weeks of healing, disrupts the recruitment of inflammatory cells and the initiation of the healing process. Judicious usage of NSAIDs is advised in all fractures, with focus of pain control with acetaminophen.

Immobilization via splinting or casting throughout healing is critical. Any fracture that has significant displacement or angulation requires reduction prior to immobilization. Postreduction images and neurovascular examination are essential. Surgery is indicated if misalignment or neurovascular complications are present or if reduction cannot be maintained. If clinical suspicion for a fracture is high but radiographs are negative, immobilize the area as if a fracture is present, and then reevaluate the patient in 10–14 days with repeat imaging. Splinting should always occur for the first 3–5 days after initial injury; circumferential casting can be applied after this time for a more permanent immobilization solution. Casting a patient during the acute inflammatory process can lead to significant morbidity through compartment syndrome or improper cast fitting after swelling resolution. Appropriate cast care instructions should be given to patients. Specific treatment management of common fractures will be addressed later in this chapter. *Fracture Management for Primary Care* [2] and *Handbook of Fractures* [3] are both excellent resources for primary care physicians who provide fracture care.

Concussion

Introduction

Concussions are defined as a traumatically induced transient disturbance of brain function resulting from either direct trauma or indirect forces to the face, head, or neck [4]. In the United

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States, over 1 million pediatric sports-related concussions occur yearly: 400,000 of these in high school athletes [5]. Symptom presentation can include a wide variety of complaints including headache, balance disturbances, retrograde amnesia, nausea, photophobia, phonophobia, visual tracking issues, slow cognition, mood changes, sleep disorders, concentration issues, confusion, dizziness, and possible loss of consciousness. Typically, symptoms begin immediately after the injury but can be delayed for up to 72 h. For adult patients, the majority of symptoms will resolve spontaneously within 14 days of injury; however, pediatric and adolescent patients may have prolonged symptoms lasting up to 4 weeks [5].

Physical Exam

Sideline evaluation should include a thorough neurological examination and cognitive evaluation in a distraction free environment. The SCAT5 [6] and Child SCAT5 [7] assessment tools are free resources to assist in initial and follow-up evaluation of concussed individuals. These tools include a brief neurological examination, a symptom checklist, a brief cognitive assessment, and a balance assessment. In the acute setting it is also important to evaluate for associated cervical spine injuries by performing cervical palpation and a range of motion examination. If at any time there is a change in the patient's neurologic status, personality, or an acute worsening of headache, this should signify the need for additional evaluation at higher level of care like the emergency room. Follow-up evaluation should focus on the patient's cognitive status, balance testing, and neurological evaluation (reflex testing, rapid alternating eye movements, visual tracking, etc.), and symptom tracking.

Imaging

Routine imaging after a concussion is not indicated. If initial evaluation findings are concerning for an intracranial bleed, a CT scan is indicated. Imaging of the cervical spine is indicated if associated injury is suspected. MRI is not commonly used in the evaluation of sport concussion but may have value in cases with atypical or prolonged recovery [5].

Management

If there is any concern for a concussion, the athlete should be removed from competition for at least the remainder of the game/day. Signs that would warrant immediate removal include loss of consciousness, impact seizure, tonic posturing, gross motor instability, confusion, or amnesia [4, 5]. Symptom checklists like those found in the SCAT5 can be helpful to monitor symptoms after a concussion. Total rest (dark room/"cocoon therapy") is no longer recommended for concussion management, and consensus guidelines endorse 24–48 h of symptom-limited cognitive and physical rest followed by gradual increase in activity, staying below the symptom exacerbation threshold [5, 8]. Currently, symptom-limited activities including activities of daily living and noncontact aerobic exercise may begin after 24–48 h and appears to improve recovery in acute concussions. Many athletes recover quickly enough to return to the classroom right away, but schools should be notified of the injury and be prepared to provide additional support to students which may include extending deadlines on assignments, extended time for test taking, or other accommodations to help with the recovery. Return to sport should always occur after return to school. Patients must perform a graded return to play protocol and must be completely symptom free before returning to play [5].

Post-concussion syndrome is now termed persistent post-concussive symptoms (PPCS) and is defined as lingering symptoms of a concussion lasting longer than the expected recovery time frame (>2 weeks for adults, >4 weeks in children) [9]. Exercises that do not exacerbate symptoms are still recommended for PPCS.

Overall, management of a concussion should be treated with a multidisciplinary approach including pharmacologic therapy, speech therapy,

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vestibular rehabilitation, physical therapy, sleep hygiene, and behavioral medicine to encompass all aspects of concussion recovery.

Acute Back Pain

History

Acute back pain is defined as less than 12 weeks of pain. Patients will often first notice the pain in the morning or develop pain after minor twisting, bending, or lifting. It is important to first rule out any red flag symptoms including progressive motor or sensory loss, recent trauma, new onset bowel or urinary incontinence, loss of anal sphincter tone, saddle anesthesia, history of cancer, or suspected spinal infection [10]. Movements that worsen symptoms such as hyperextension should be noted in youth athletes, especially weightlifters, cheerleaders, and gymnasts.

Physical Exam

Physical exam should include inspection, palpation, range of motion of the lumbosacral musculature, hamstring and hip flexor flexibility, and a lower extremity neurologic exam. Palpation assists in determining if the symptoms are secondary to bony or muscular pathology. Flexibility testing of the hamstrings and hip flexors can assist in determining underlying biomechanical causes for the patient's pain. The straight leg test is commonly used for evaluation of radicular symptoms (sciatica). The test has high sensitivity but poor specificity. Loss of normal lumbar spine lordosis, tight hamstrings, and vertical position of the patient's sacrum are diagnostic clues in identifying acute spondylolysis [11].

Imaging

Without red flag findings, diagnostic imaging is not indicated. If signs or symptoms of fracture are present, then plain films including AP, lateral, and oblique views are the initial imaging of choice.

Management

Treatment should first focus on patient education and expectations, discussing that patients often need little intervention for improvement. Acetaminophen and NSAIDS are first line. In patients with muscle spasms, a short course of muscle relaxants is appropriate. Opioids should be avoided in the first episode of moderate low back pain as studies have shown no benefit of opioids compared to NSAIDs [12]. Often the pain resolves within a few weeks to few months with or without treatment. Episodes that last longer than 6 weeks have a poorer prognosis. Patients should be reminded to stay active, avoid aggravating movements, and return to normal activity as soon as possible. Early physical therapy may lessen the risk of recurrence and need for healthcare services [10]. OMT, acupuncture, superficial heat, and massage can be beneficial as well [12].

Rotator Cuff Injuries

History

Patients commonly complain of anterolateral shoulder pain that can radiate to the lateral arm that is exacerbated by overhead movements. Additionally, patients will often present with nocturnal pain occurring when lying on the affected shoulder. While some rotator cuff injuries occur from an acute injury, most result from cumulative microtrauma. Weakness may be present with rotator cuff injuries. Participating in overhead sports (baseball, swimming, weightlifting) and having a job that performs repetitive overhead tasks are risk factors for rotator cuff injuries.

Physical Exam

Inspection can reveal scapular dyskinesia and/or muscle atrophy of the supraspinatus or infraspinatus of the affected side. Palpation of the lateral shoulder over the subdeltoid bursa and rotator cuff insertions may elicit pain. Active range of motion will be decreased compared to

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passive range of motion. Special tests have been developed to test specific rotator cuff muscles. The drop arm test looks for a gross tear in the supraspinatus. The patient fully elevates their arm in the scapular plane and then tries to lower it slowly. A sudden drop in the arm would suggest a major tear. Jobe's "empty can" test evaluates the supraspinatus integrity as well. In this test, a downward force is applied to a humerus that has been abducted to 90°, forward flexed 30°, and pronated till the thumb is pointed down. Both the teres minor and infraspinatus are tested with resisted external rotation with the arms at the patient's side and elbow flexed to 90°. Subscapularis strength can be assessed with the "belly press." The patient is instructed to place their palm on their umbilicus and resist the examiner from pulling his/her hand off their abdomen. In all of the specific tests, pain without weakness suggests a tendinopathy, but pain with weakness should make the clinician consider a more substantial injury [13].

Imaging

Radiographs consisting of three views of the shoulder (AP, axillary, and scapular Y) may be obtained to assess the shoulder for joint degeneration, fractures, positioning of humeral head in relation to rest of shoulder joint, and soft tissue calcifications. A finding such as a "high riding humerus" (<7 mm from humeral head to acromion) is suspicious for a rotator cuff tear. If a detailed evaluation of rotator cuff anatomy is desired, an MRI should be considered.

Management

Acute full-thickness rotator cuff tears should be referred to an orthopedist for surgical evaluation. Physical therapy is the cornerstone of conservative management for all other injuries [14, 15]. Rehabilitation exercises should focus on restoring shoulder range of motion, correcting shoulder biomechanics through rotator cuff strengthening and scapular stabilization, correcting poor static and dynamic posture, and providing graded loading [14]. A short (7–10-day) course of NSAIDS and activity modification such as limiting overhead activities can complement the rehabilitation process by decreasing pain in the short term. Steroid injections are a commonly used option to decrease inflammation, but judicious use is advised. The benefit of decreased inflammation must be balanced against potential articular cartilage and rotator cuff damage from the components of the injection. As with all musculoskeletal injections, emphasis should be placed on appropriate rehabilitation in conjunction with the injection.

Shoulder Instability

History

The term shoulder instability is defined as symptomatic, abnormal translation of the humeral head on the glenoid [13] and may be due to an acute dislocation or repetitive microtrauma. This instability can then be classified by the direction of that instability (anterior, posterior, inferior, or multidirectional planes). For instability caused by dislocations, the overwhelming majority of shoulder dislocations occur in the anterior direction. Patients will often describe some type of force being applied to their upper arm while it is abducted and externally rotated. Posterior dislocations occur rarely and are associated with electrocutions or seizures. Chronic shoulder instability can also occur, and it is typically the result of prior dislocations or nontraumatic repetitive microtrauma. Athletes with repetitive overhead motions such as swimmers, baseball pitchers, and volleyball players are at increased risk of chronic instability. With acute dislocations, the patient will describe a popping sensation with subsequent pain and obvious gross deformity. In athletes with chronic instability, the patient will often describe pain and a feeling of shoulder instability with certain overhead movements. Overhead throwing athletes will also express a feeling of decreased throwing/hitting velocity. Associated soft tissue trauma to structures such as the labrum and rotator cuff are known complications of shoulder instability.

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Physical Examination

Gross shoulder deformity will be present with dislocations. Positioning of the patient's arms will be different with an anterior injury (slight abduction and external rotation) versus a posterior injury (adduction and internal rotation). Apprehension with movement will be universal. It is imperative to assess integrity of the axillary nerve; impaired function heralds more urgency in reduction. Testing sensory distribution over the patient's deltoid can easily assess axillary nerve function.

In chronic instability, determining the direction of instability (anterior, posterior, inferior, or multidirectional) is needed to allow appropriate treatment. Joint laxity testing can be completed using multiple testing maneuvers looking for either anterior (apprehension, relocation, and load and shift tests), posterior (load and shift, posterior stress test, jerk test), or inferior (sulcus sign) instability [13]. The labrum should also be examined as there are frequently concurrent injuries to the labrum with shoulder instability. Labral examination techniques include dynamic sheer, passive distraction, biceps load, and O'Brien's [13].

Imaging

Standard shoulder radiograph (AP, lateral, scapular Y) should be ordered with all shoulder traumas. Radiographs allow visualization of the direction of dislocation and associated fractures such as a Hill-Sachs (cortical depression of humeral head caused by glenoid rim) or bony Bankart lesion (fracture of anterior inferior glenoid) [16]. Radiographs are not acutely necessary before all reductions but are recommended after all reductions.

Treatment

Reduction of the dislocated shoulder should be completed as soon as possible. Delayed treatment will allow the patient's shoulder musculature to spasm to the point where conscious sedation may be required to complete the reduction. Techniques for anterior shoulder reductions can be broken down into two broad categories: traction and leverage. Traction options include the Hippocratic technique, Stimson technique, and scapular manipulation technique. Leverage techniques include Kocher's technique and Milch's technique [17]. Stimson's method is a relatively non-traumatic technique that is easy to complete field side. The patient should lie prone on an exam table or bench with the affected arm hanging off the table. Gentle downward traction is applied in order to facilitate the relaxation of muscles and spontaneous reduction [17]. Relocation of a posterior dislocation is done with patient supine. Traction is applied to the affected arm, while forward pressure is applied to the humerus [13]. After reduction, the patient should then be immobilized in a sling for 2–4 weeks with early physical therapy or potential surgical intervention. Positioning (internal rotation versus external rotation) of the arm during immobilization remains controversial; however, some studies have shown superior outcomes with the shoulder placed in external rotation when compared to internal rotation [18]. Surgical consultation for discussion of operative treatment options should be considered in young athletes after their initial dislocation; the risk of recurrent dislocation is approximately 90% if initial event occurs prior to the age of 20 [17]. In a systematic review, it was found that there was a 9.6% recurrence rate of dislocation after arthroscopic reconstructive surgery versus. 37.5% recurrence in conservative therapy groups [18]. Return to play in athletes after surgical stabilization is typically 4–6 months [13].

Aggressive physical therapy with strengthening of the rotator cuff and scapular stabilizing muscle remains the mainstay of treatment for chronic instability. Bracing options are available but often limit the patient's range of motion too excessively. Surgical options are available for unidirectional anterior or posterior instability if conservative measures fail. Operative results for multidirectional instability have not

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mirrored those of unidirectional instability but can be discussed if the patient fails conservative management [13].

Bicep Tendon Ruptures

History

Bicep tendon ruptures can occur at the long head origin within the labrum, the short head origin on the acromion, or the common distal insertion. The long head is the most common rupture site; it commonly occurs after forceful elbow flexion against resistance. Acute ruptures classically present with a sudden pop, followed by pain, ecchymosis, and swelling. In a long head rupture, pain will often originate in the anterior shoulder with radiation into the belly muscle.

Physical Exam

Patients with a proximal tendon rupture will present with swelling and ecchymosis in the upper and middle region of the bicep as well as tenderness over the anterior shoulder [19]. Loss of normal arm contour caused by the distal migration of the biceps muscle belly will give the classic "Popeye deformity," where the bicep will be more prominent over the middle of the humerus compared to the unaffected side with elbow flexion. There may also be a slight decrease in the strength of elbow flexion and forearm supination [13]. Distal bicep tendon ruptures will present with swelling and ecchymosis over the antecubital fossa along with a lack of musculature over the distal humerus. A noticeable decrease in strength will be noted with Speed's and Yergason's test [20].

Imaging

Shoulder or elbow films should be ordered depending on the injury site to evaluate for associated bone injury. Distal tendon injuries should be evaluated with MRI or musculoskeletal ultrasound of the upper extremity/elbow. Given the long head tendon's origin with the labrum, patients with proximal injuries and associated shoulder pain/instability should undergo MRI arthrogram of the shoulder to identify any associated labrum injuries.

Management

Proximal bicep tendon ruptures can be managed nonsurgically with referral to physical therapy. Physical therapy improves the strength and flexibility of the biceps and shoulder musculature, which often contributes to the patient's symptoms. If an associated labrum injury is found and the patient does not respond to physical therapy, a referral to orthopedic surgery should be placed. All distal biceps tendon tears should be referred immediately to an orthopedic surgeon for early primary repair.

Lateral Epicondylitis "Tennis Elbow"

History

Patients will regularly present with pain in the lateral elbow and upper forearm. The pain often begins after a recent increase in physical activities that require repetitive wrist extension and supination. Common inciting activities include weightlifting and racquet sports such as tennis, badminton, squash, or racquetball. Patients may also complain of decreased grip strength.

Physical Exam

Palpation will elicit point tenderness at lateral epicondyle and along the distal extensor carpi radialis brevis (ECRB) tendon. Resisted wrist extension, wrist supination, and third-digit extension with forearm in pronation will be painful. Decreased grip strength versus the unaffected side may be present also. Sensory exam should be normal. Radiation of pain from the lateral epicondyle into the proximal forearm and

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associated weakness with the above resisted testing should raise suspicion of an alternative diagnosis such as radial tunnel syndrome [19, 21].

Imaging

Plain films of the elbow can evaluate for fracture, tendon calcification, osteochondral defects, or radial head arthritis. Ultrasound can help identify chronic tendinosis within the origin of the ECRB.

Management

The vast majority of lateral epicondylitis cases can be managed nonsurgically [22]. Activity modification is a key component of treatment. Decreasing or stopping the instigating motions or modifying equipment such as using a wider grip on a tennis racquet can assist in managing symptoms. Physical therapy (eccentric-based exercises), NSAIDs, steroid injections, and counter load braces have been the mainstay of conservative treatment [20], but currently the use of corticosteroids is being debated [22]. Increasing evidence shows that prolonged lateral epicondylitis (greater than 4–6 months) is a tendinosis instead of tendinitis, thus calling into question the usage of NSAIDs and steroid injections in its management [33]. New treatment techniques such as dry needling, prolotherapy, autologous blood injection (ABI), and platelet-rich plasma (PRP) are emerging as treatment options [21]. There is no clinical consensus on the most efficacious treatment plan at this time [22] with multiple modalities helping improve long-term outcomes. Recalcitrant cases (greater than 18 months of symptoms without response) can be referred to orthopedics for possible operative debridement [21].

Scaphoid Fracture

History

The most common mechanism of injury involves a fall on the outstretched hand (FOOSH injury). Less frequently a sudden axial load through the wrist can cause a scaphoid fracture [23]. The patient will endorse deep, dull pain in the radial wrist. The pain is exacerbated by gripping or squeezing. A patient with radial wrist pain after an injury should be managed as if there is a scaphoid fracture until proven otherwise [24].

Physical

The patient may exhibit only mild swelling over the anatomic snuffbox. Pain is reproducible with palpation of the anatomical snuffbox. Patients can often still move the wrist, with pain elicited at the extremes of radial and ulnar deviation. Axial compression of the thumb will also elicit pain. Watson's shift test should be completed to evaluate for scapholunate dissociation. The assessment of median nerve function is needed to exclude associated injury.

Imaging

Initial imaging should include clenched fist PA, lateral, scaphoid, and oblique views. The scaphoid view puts the wrist in ulnar deviation and allows better visualization of the proximal scaphoid. The clenched fist view evaluates for scapholunate dissociation, with greater than 4 mm of space between the scaphoid and lunate being abnormal. If there is concern for scapholunate dissociation on initial films, a comparison view of the contralateral wrist should be obtained for comparison.

Management

Management depends on the location of the scaphoid fracture given the bone's tenuous retrograde blood supply. Indications for an orthopedic referral include greater than 1 millimeter (mm) of displacement, fracture comminution, scapholunate angle greater than 60°, scapholunate disassociation, and greater than 10 degrees of angulation [25]. Successful healing with nonoperative treatment occurs in 100% of distal third and tuberosity fracture, 80–90% of waist

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fractures, but only 60–70% of proximal fractures [25]. Early consultation with orthopedic surgery should be strongly considered in proximal third fractures because of significant morbidity from malunion, nonunion, and/or avascular necrosis [25].

If the decision is made to treat the patient nonoperatively, the exact type of cast (short arm thumb spica versus long arm spica) for the initial immobilization depends on fracture type. For each type, repeat imaging should be obtained every 2–3 weeks until radiographic union is observed. Nondisplaced distal fractures require 6–8 weeks for healing. Patients should be immobilized in a short arm thumb spica cast for 4–6 weeks. Additional time may be required if clinical union is prolonged. Middle third and distal third fracture should be immobilized with a long arm thumb spica cast for 6 weeks followed by a short arm thumb spica cast for an additional 6 weeks. Healing times for middle third/waist fracture range from 8–12 weeks, while proximal fracture healing usually requires 18–24 weeks. Due to the prolonged immobilization times required for most scaphoid fractures, patients will likely benefit from physical or occupational therapy to expedite a safe return to work or sports [25].

Patients will often present after a FOOSH injury, but their initial imaging will be negative. If a scaphoid fracture is suspected, place the patient in a thumb spica splint or brace for 2 weeks and then repeat films. At that point, there may be bone changes around a previously unrecognizable fracture. If follow-up plain films are still negative, additional imaging with MRI is indicated if clinical suspicion for a scaphoid fracture remains.

Boxer's Fracture

History

A boxer's fracture is the fracture of the 5th metacarpal neck, most commonly caused by punching a firm object or wall with a clenched fist. The patient will often present with pain and edema over the dorsum of the hand.

Physical

On exam, there may be loss of knuckle contouring. In severe angulation, pseudoclawing may present. It is imperative to evaluate for malrotation. In a semiflexed position, the plane of the fingernails should all be aligned and in full flexion; all fingers should point toward the scaphoid tubercle [26]. The hand should also be examined for teeth marks that resulted from a punching injury as that could be a source of infection.

Imaging

Plain radiographs should be obtained in the anteroposterior, lateral, and oblique views. The lateral view is used for measurement of apex dorsal angulation. When calculating the angulation, keep in mind the metacarpal neck at baseline has 15 degrees of volar angulation [27].

Management

Fractures with malrotation or angulation greater than 40–50° should be referred to orthopedics [27]. The patient should be placed in an ulnar gutter splint with the MCP in 70–90° flexion and PIP and DIP in slight flexion until seen by specialist.

In the absence of malrotation, an attempt for reduction can be made. Most patients require an ulnar or hematoma block prior to a reduction attempt. Reduction is performed by flexing the MCP joint to 90°, applying dorsally directed pressure to the volar displaced metacarpal head and volar directed pressure to the proximal fracture fragment. After reduction, the finger should be splinted as stated above. Repeat radiographs should be obtained within 1 week to assess for angulation or malrotation. Afterward radiographs should be obtained every 2 weeks following, until clinical and radiographic healing is present, typically between 4 and 6 weeks [26]. If the fracture has significantly more angulation or the reduction has slipped, the patient should be referred to orthopedics. After immobilization, it is important the patient start ROM exercises and handgrip strengthening.

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Mallet Finger

History

The injury is caused by an avulsion of the extensor tendon from the dorsum of the base of the distal phalanx with or without an avulsion of a bony fragment. The mechanism of injury occurs when the distal interphalangeal (DIP) joint that is being extended is suddenly forced into a flexed position. This commonly occurs when an object (usually a ball) strikes the extended finger.

Presentation and Physical Exam

Patients typically present with pain at the dorsal DIP, inability to actively extend the joint, and possible flexion deformity. For the exam, the physician should stabilize the proximal interphalangeal (PIP) joint, and the patient will be unable to fully extend his or her DIP joint. Providers should assess passive range of motion of the DIP as well to assess for possible bony or soft tissue entrapment. As with all finger injuries, the assessment of associated joint collateral ligaments, finger alignment, and possible rotational deformity should be assessed.

Imaging

AP, lateral, and oblique views of the finger should always be obtained to determine if bony avulsion has occurred as that may change the management of the injury. Radiographs may be normal if just soft tissue structures are affected.

Management

The majority of mallet finger injuries can be managed conservatively. Indications for surgical referral are controversial but include inability to adequately reduce the avulsed fragment, volar subluxation of the DIP joint, inability to obtain full passive extension of the DIP, and greater than 30% of the articular surface of the DIP being involved [26, 28]. Conservative treatment consists of splinting DIP in full extension for 6 continuous weeks. Flexing of the DIP at any time, even with splint changes, will cause the 6-week clock to start over. After the initial 6-week period of splinting, an additional 6-week period of nocturnal and activity splinting should be completed. Multiple different splints are available for the treatment of mallet finger; no splint type is superior but needs to be robust enough for daily wear [29].

Jersey Finger

History

Jersey finger is the rupture of the flexor digitorum profundus (FDP) tendon from the distal phalanx. The injury is caused by forced passive extension of the DIP joint during active flexion. This commonly occurs when an athlete's finger catches on another player's clothing, most often during football and rugby. The FDP of the 4th digit is affected in 75% of the cases [26].

Physical

The patient will present with pain and swelling at the palmar aspect of the DIP joint, and ecchymosis may be present depending on timing of presentation. The affected finger may lay extended with the hand at rest. During exam, it is imperative that the DIP joint is isolated. The patient will have a loss of active DIP joint flexion and an inability to make a fist. Finger alignment and rotation should also be assessed [26].

Imaging

PA and lateral view radiographs may show an avulsed bony fragment or fractures. Ultrasound can show a retracted tendon rupture [23].

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Management

The diagnosis of jersey finger requires urgent referral to orthopedics as prognosis worsens with delayed treatment. The involved finger should be splinted in a flexion until the patient is seen by orthopedics [26].

IT Band Syndrome

History

Iliotibial band (ITB) syndrome is an overuse injury that usually causes pain around the lateral femoral condyle; however, the patient can endorse pain anywhere along the IT band. The classic presentation is an active young person with lateral knee pain that increases through physical activity. Early in disease process, symptoms occur at the completion of a repetitive flexion/extension exercise. As the condition worsens, pain is often experienced earlier in activity and may begin to be present at rest. ITB issues commonly occur in runners, cyclist, soccer players, and basketball players.

Physical Exam

Inspection of the lower extremity anatomy can help determine if a person is predisposed to IT symptoms. Anterior pelvic tilt, genu varum, excessive foot pronation, and leg-length discrepancy can predispose the patient to chronic IT band irritation. The patient will likely have tenderness on palpation at the distal portion of the ITB where it courses over the lateral femoral epicondyle or Gerdy's tubercle. Ober's test reveals IT band tightness and the patient usually has a limitation of hip abduction [30]. Gait analysis may reveal a Trendelenburg gait, an indication of hip abductor weakness. Single-leg squat may also reveal subtle strength deficits in the abductors and quadriceps which can add to overload of the ITB.

Imaging

ITBS is a clinical diagnosis, and additional diagnostic studies are not necessary; however, if pain is located distally, anterior-posterior, lateral, and sunrise radiographic views of the knee can reveal arthritic changes within the knee or patellar malalignment.

Treatment

The initial goal of treatment is to reduce local inflammation and provide effective pain relief with stretching, ice, and NSAIDs. The patient can also use a foam roller to break up soft tissue adhesions in the ITB. Activity modification is essential. In mild cases, educate the patient to stay below the time or distance at which the symptoms start. In more severe cases, patients should avoid all aggravating activity. The patient can change to lower impact activities such as swimming or elliptical. Treatment should focus on correcting underlying biomechanical symptoms. Physical therapy is important as the patient should focus on strengthening pelvis/core stabilizers and improving strength and flexibility of the hamstrings. Excessive foot pronation can be corrected with appropriate orthotics. Corticosteroid injection at the lateral femoral condyle can be considered in severe cases [30].

Patella Dislocation

History

The most common mechanism for lateral patellar dislocation is typically during sport where the foot is planted and an internal rotary force is applied to the flexed knee in a valgus position (e.g., spinning, swinging a baseball bat, or quick lateral change of direction while running). Patients may complain of their knee "giving out" followed by severe pain and deformity that may or may not be accompanied by a "popping" sound. Pain and

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swelling are typically seen post dislocation, and many cases spontaneously reduce with knee extension. Injuries may be from an acute event or from repetitive microtrauma. History and complaint of recurrent patellar subluxation are other significant clinical clues.

Physical Exam

After an acute injury, a large knee effusion will be present. Significant hemarthrosis increases the chance that an osteochondral injury occurred [31]. An obvious deformity will be seen if relocation has not occurred. If relocation has occurred, the medial retinaculum/medial edge of the patella and the lateral femoral condyle are often tender to palpation. A positive patellar apprehension test will be noted, and laxity in patellar movement will also be observed.

Imaging

Radiographs are not necessary prior to reduction unless the diagnosis is in question. Standard three-view knee (AP, lateral, sunrise) films should be obtained to assess for fractures postreduction. If the exam does not ensure intact knee ligaments, a large hemarthrosis is present, or a fracture is seen on radiographs, then an MRI is indicated to look for associated ligamentous or meniscal injury [31].

Management

In the event that the patella has not been relocated, reduction should be accomplished. To reduce the patella, flex the hip, and apply a medial force to the patella while fully extending the knee. Immobilization of the knee in full extension should occur after reduction, and the patient should be non-weight bearing for 2–3 days until follow-up appointment. Currently, there is no consensus on length of immobilization but can range from 1–6 weeks. Non-weight-bearing status can typically be discontinued as tolerated by the patient. Controversy exists on surgical versus conservative management on primary traumatic patellar dislocation [32]; however, it is reasonable to begin with nonoperative management. Palpable defects of the parapatellar ligament structures, recurrent subluxation on initial examination, and findings of osteochondral lesion on imaging are indications for referral to orthopedic surgery. Physical therapy can assist the patient in regaining full range of motion and address underlying quadriceps' weakness to prevent recurrent dislocations or subluxations. Knee braces with patellar sleeves or a lateral J brace can assist athletes in regaining confidence in their knee; however, there is a lack of evidence supporting this practice. After the first dislocation, patients have approximately a 50% chance of recurrence or instability [33]. Patients with recurrent dislocations should be evaluated by an orthopedist [31].

Knee Ligament Sprains/Tears

History

The knee consists of four major ligaments; each has its own injury history and associated exam findings.

Anterior Cruciate Ligament (ACL): The ACL runs from its origin on the posteromedial aspect of the lateral femoral condyle to its insertion on the intercondylar tibial eminence; its main function is to prevent anterior translation of the tibia. ACL injuries most commonly occur without contact and during a sudden change in direction or pivot such as skiers and soccer players. This mechanism can occur with hyperflexion or hyperextension of the knee as well as when initiating or landing a jump. In contact sports such as football, injury of the ACL can occur in association with MCL and medial meniscus injuries, known as the "unhappy triad," after a valgus force is applied to a planted foot. The patient may report a "pop" sensation followed by significant swelling within 2 h after an acute injury [34]. Delayed presenters complain of a feeling of instability or "giving way" of the knee with twisting, pivoting, and cutting. Female athletes are at a higher risk for ACL injuries

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compared to male athletes secondary to an increased Q angle, quad dominance, decreased knee and hip flexion with landing, and hormone status [35].

Posterior Cruciate Ligament (PCL): The PCL runs from the posterior tibia to its insertion on the anteromedial aspect of the medial femoral condyle; the main function of the PCL is to prevent posterior translation of the tibia. PCL mechanism of injury is hyperextension from a posterior force or hyperflexion with plantar flexion of the ankle. The classic mechanism of injury is a dashboard injury of the knee during a motor vehicle accident. The most common complaint from the patient is instability of the knee.

Medial Collateral Ligament (MCL): MCL injury is a result of the lateral force to the knee with an anchored foot that creates a valgus stress. Patients will sometimes describe instability but will most often complain of swelling and pain along the medial joint line.

Lateral Collateral Ligament (LCL): An LCL injury is uncommon, but when it does occur, it is often associated with a PCL injury. Excessive anteromedial knee force when the knee is fully extended can stress the LCL. Patients will complain of pain over the lateral joint line and may feel instability with twisting, cutting, or pivoting. Patient will sometimes complain of lateral leg numbness and weakness with ankle dorsiflexion secondary to associated peroneal nerve injury.

Physical

ACL: Examination for potential ACL injury is best done immediately after the suspected injury before subsequent hemarthrosis and muscle guarding limit the exam. Significant knee effusion will occur within hours of injury. The most accurate test of an ACL injury is the Lachman test with a sensitivity of 87% and specificity of 97% [36]. Anterior drawer test is not as reliable as it can be falsely positive secondary to a PCL injury [34]. Meniscal integrity should also be checked as ACL tears often have associated meniscus tears.

PCL: Examination will show an effusion and tenderness within the popliteal fossa. The posterior drawer test is the exam of choice. If the posterior drawer test is positive, Dial's test should be completed to evaluate for posterolateral corner (PLC) injury [37]. Positive MCL/LCL testing at full extension is also suggestive of a PCL injury [34].

MCL/LCL: Assess for laxity in these ligaments with the knee in full extension and at 30 degrees of flexion with varus and valgus stress testing.

Imaging

X-rays should be obtained to assess for fractures. MRI is indicated in suspected ligament or meniscal tears where operative treatment would be indicated.

Management

ACL: Initial management includes rest, ice, compression, and elevation (RICE) along with crutch and brace usage. Weight bearing should be avoided early on as ACL is often associated with significant bone contusions. Range of motion exercises should be started as soon as pain allows. Referral to orthopedics for discussion of operative management should be made but is not emergent as surgery is often delayed allowing for resolution of hemarthrosis and increased range of motion. The American Academy of Orthopedic Surgeons (AAOS) recommends 12 weeks of nonoperative treatment for acute isolated ACL tears then reevaluation for need of surgery [35].

PCL: Surgical management is deferred unless other associated injuries such as a PLC injury occurred. Early range of motion and quadriceps strengthening should be encouraged for grade 1 and 2 injuries. Grade 3 injuries respond to immobilization in knee brace for a few weeks followed by formal physical for 3–4 months. Surgical referral should occur if the patient fails conservative management [34].

MCL/LCL: Initial management includes RICE and physical therapy. Grade 3 injuries (significant joint line gapping on varus/valgus testing) should be evaluated by an orthopedist, as they are often

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associated with other soft tissue injuries such as meniscal, PCL, or PLC injuries.

Meniscus Tear

History

A meniscus tear typically occurs from a traumatic forceful twisting or hyperflexion of the knee (squatting); however, chronic degenerative tears can result from years of stress and may have no acute mechanism. Meniscal injuries are also associated with other traumatic injuries such as ACL and PCL injuries. Patients may complain of mechanical symptoms such as their knee locking or buckling. Swelling after an acute injury presents 48–72 h after the trauma; however, most meniscus injuries are secondary to chronic microtrauma and will have minimal swelling.

Physical Exam

Joint line tenderness is a common finding on examination. Specialized tests including McMurray test, Apley's Compression test, and Thessaly test can assist in diagnosis. In general, one cannot make a definitive diagnosis with a single positive or negative special test.

Imaging

Knee X-rays should be obtained to assess for associated fracture especially with an acute/traumatic injury. If surgical intervention is being considered, then an MRI is warranted as it has a sensitivity of >90% for evaluation of meniscal tears [34].

Management

RICE and physical therapy will treat most chronic meniscal injuries. Steroid injections can be considered to assist in pain management during physical therapy. Indications for orthopedic referral include acute traumatic meniscus injuries and chronic injuries with mechanical symptoms.

Patellofemoral Pain Syndrome

Introduction

Patellofemoral pain syndrome (PFPS) is defined as a pain occurring around or behind the patella that is aggravated by activities that load the patella during weight-based activities on a flexed knee [38]. Pain is typically exacerbated with activities including running, climbing stairs, jumping, and squatting. Risk factors are thought to include female sex, decreased quadriceps strength, and patellar maltracking [39].

Physical Exam

Patients may complain of pain or stiffness after prolonged sitting with knee flexion sometimes known as the "theater sign." Large joint effusions and erythema are typically not seen with PFPS. Patellar maltracking or lateral deviation may be noted on exam. Multiple exam maneuvers can be used to aid in diagnosis including the Clarke test, patellar grind, pain during squatting, and pain with palpation of the medial or lateral patellar facet palpation. Additionally, the patient's gait, posture, and footwear/foot mechanics should be observed to look for potential exacerbating symptoms.

Imaging

PFPS is a clinical diagnosis, but imaging may be used to help rule out other pathologies. If radiographs are ordered, typically AP, lateral, and sunrise or Merchant views are ordered. MRI is typically not a standard component in the evaluation of PFPS.

Treatment

Initial treatment should focus on pain relief which may be accomplished through relative rest, ice, and NSAIDs, but physical therapy is the cornerstone of treatment. Due to multiple

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contributing factors to PFPS, no one set physical therapy regimen is recommended. Instead, treatment should be individualized to each patient [40]. While going through physical therapy, patients should remain physically active and should continue flexibility and strengthening exercises even after physical therapy has been completed.

Achilles Tendon Rupture

History

Achilles tendon ruptures are frequently seen in athletes, especially weekend warriors. The injury usually occurs during a push-off during running or a lateral movement. Patients may hear a "pop" or feel a snap sensation in their posterior ankle followed by significant pain.

Physical Exam

On inspection of the posterior lower leg, swelling and ecchymosis will be present. A palpable defect in the heel cord may be appreciated but can be unreliable in the presence of pain. The most reliable finding is a loss of resistance to passive dorsiflexion or loss of active plantar flexion; however, a patient may be able to still plantarflex because the other plantar flexors are still intact [41]. Thompson's test is diagnostic for a complete Achilles tendon rupture. It is performed by having the patient lie prone and flexing the knee to 90°. The gastrocnemius should be squeezed and look for ankle plantar flexion. Absence of plantar flexion is indicative of a full rupture. With a partial tear, the Thompson test may be positive or negative.

Imaging

MRI is the imaging modality of choice, especially for preoperative planning. Musculoskeletal ultrasound may also be helpful.

Management

Initial management includes non-weight-bearing status with the injured lower extremity splinted in a posterior splint with the ankle in plantar flexion. All patients need immediate referral to orthopedic surgery for discussion of definitive management. Management is controversial and often depends on the patient's comorbidities and goals, but ruptures can be managed both nonoperatively and operatively [41].

Achilles Tendinopathy

History

As with other tendon injuries discussed in this chapter, injuries can range from an acute inflammatory process (tendinitis) to a chronic injury with dysfunctional tendon healing (tendinosis). Patients will complain of pain in their distal Achilles at its insertion, or more commonly 2–6 cm proximal to the insertion [42]. Pain typically starts at the beginning or end of exercise, but as the condition progresses, the pain can persist throughout the entire duration of exercise. Pain often worsens with sudden acceleration, jumping, prolonged walking/jogging, or with calf stretches. A history of recent change in exercise intensity or style of training will sometimes be described by the patients as well.

Physical Exam

Minimal swelling will be seen on exam. A patient will be tender to palpation along the distal Achilles tendon. Occasionally, nodules will be palpated over the distal Achilles as well. Limited ankle dorsiflexion may be noted secondary to tight gastrocnemius/soleus complex. Pes planus can also be seen on exam. The Thompson test can also be performed to assess the integrity of the Achilles tendon to rule out a complete tear.

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Imaging

No imaging is indicated, as this is a clinical diagnosis. If the clinician is concerned about a possible partial tendon tear, MRI can be considered. Additionally, ultrasound is increasingly being used as a quick bedside tool to assess tendon integrity and appearance.

Management

Treatment options depend on the location of symptoms. Initial management includes risk factor modifications, relative rest, and location-specific rehabilitation exercises. Midportion tendinopathy is treated with eccentric exercises to start and then a combination of eccentric and concentric exercises [42]. Insertional tendinopathies are harder to treat and do not respond as well to eccentric exercise programs. Therefore, the main focus of rehab in insertional pathologies is concentric exercises [42]. Heel lifts or orthotics can also be added to the patient's shoes to help correct foot malalignment (typically pes planus). If the patient fails to demonstrate any improvement with conservative treatment and a short course of therapy, other modalities such as extracorporeal shock wave therapy, PRP injections, and topical nitroglycerin may be tried [42]. Steroid injections should be avoided in the management of Achilles tendinopathy given the associated increase in tendon rupture. Surgical evaluation should be reserved for severe cases that do not improve after 6 months or more of conservative management.

Ankle Sprain

History

Ankle sprains can be broken down into lateral, medial, or syndesmotic "high ankle" sprains. Most ankle sprains are injuries to the lateral ligaments of the ankle caused by inversion of the ankle. Inversion injuries will most commonly damage the anterior talofibular ligament (ATFL). This type of injury is common in basketball, soccer, and football. Medial ankle injuries are uncommon and involve eversion of the planter-flexed foot. This mechanism leads to injury to the deltoid ligament and will often lead to lateral malleolus fractures. High ankle sprains occur when a hyper dorsiflexed ankle is forcibly externally rotated. This type most commonly occurs in football, wrestling, and ice hockey and will damage the anterior inferior tibiofibular ligament (AITFL) [43]. Disruption of the AITFL can led to disruption of the dense connective tissue between the tibia and fibula, i.e., syndesmosis. For all types of ankle sprains, the patient will often complain of immediate pain, swelling, ecchymosis, and difficulty with ambulation.

Physical Exam

On inspection of the ankle, significant ecchymosis and effusion will often be present with all types of ankle injuries. Limited ankle range of motion will also be seen [44]. Palpation should occur over the bony landmarks of the Ottawa ankle rules. Palpation should also occur over the main ligaments of the ankle (ATFL, AITFL, calcaneofibular ligament (CFL), posterior talofibular ligament (PTFL), and the deltoid ligament. Tenderness to palpation of the ATFL and CFL is often found on lateral ankle injuries.

Several special tests exist for the ankle. The anterior drawer test and the talar tilt test can assist in the diagnosis of lateral ankle sprains. For high ankle sprains, the external rotation test, tenderness over the AITF, and the squeeze test should be performed to confirm diagnosis [45].

Imaging

The Ottawa ankle rules should be used to determine the appropriateness of imaging. Ottawa ankle rules are nearly 100% sensitive for detecting fractures in adults and children as young as 5 years [44].

X-rays are indicated only if any of the five physical exam findings are present:

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- Inability to bear weight for four steps immediately after the injury or in the exam room
- Bony tenderness over the posterior aspect of the medial malleolus
- Bony tenderness over the posterior aspect of the lateral malleolus
- Bony tenderness over the base of the fifth metatarsal head
- Bony tenderness over the navicular

Standard plain films of the ankle should include AP, lateral, and mortise views. The mortise view is essential to evaluate ankle joint stability. Physicians should consider obtaining additional plains of the proximal tibia and fibula on high ankle sprain patients with a positive squeeze test for a possible Maisonneuve fracture of the proximal fibula.

Management

Grade 1 and 2 lateral ankle sprains should be treated with RICE. Range of motion exercises or formal physical therapy should be initiated within the first 48 h. These injuries will typically heal within 1–4 weeks. Grade 3 injuries may require a short period of time in a CAM boot until full weight bearing is tolerated. In the rehabilitation period following, a semirigid or lace-up brace should be worn. Grade 3 injuries can take 5–8 weeks to heal and require up to 6 months for full rehabilitation [44]. Patients with significant ankle sprains should be reexamined in 4–6 weeks to assess for symptoms or findings of ligamentous instability. Surgical referrals to orthopedics should be reserved for chronic pain, chronic instability, and inability to return to previous functional level after an appropriate rehabilitation course. Consideration should be made for athletes to wear a lace-up ankle brace with Figure 8 straps after returning to competition.

High ankle sprains require additional immobilization compared to lateral sprains. Immobilization in a walking boot for 3–4 weeks with progressive increase in weight bearing is often needed. Formal physical therapy should begin immediately after injury. Return to athletics can take anywhere from 4 to 8 weeks depending on the severity of the injury. Providers must ensure that the patient's plain films did not demonstrate a widened mortise, as this indicates an unstable ankle joint and will require surgical fixation [46].

Proximal Fifth Metatarsal Fracture

Introduction

Proximal fifth metatarsal fractures can classically be divided into three different types based off of anatomy and history. The three anatomical areas include the metatarsal tuberosity, metaphyseal/diaphyseal junction, and proximal diaphysis, and the mechanism of injury and treatment will differ depending on the affected region.

History

Injuries to the tuberosity are typically avulsion type injuries from either the plantar fascia or peroneus brevis attachment, and the mechanism is typically an ankle inversion with the foot in plantar flexion. Acute metaphyseal/diaphyseal junction injuries (Jones Fracture) typically result from a vertical or mediolateral force placed on the base of the fifth metatarsal with the patient's weight over the lateral aspect of their foot, most likely with their foot in plantar flexion. Finally, diaphyseal stress fractures typically are caused by chronic overloading. A good history is imperative as acute fractures and stress fracture that evolved into occult injuries require different durations of treatment.

Physical Exam

Weight bearing will often be difficult. Patients will generally have pain over the lateral border of the forefoot, exaggerated with weight bearing. Resisted foot eversion will increase pain. Point tenderness at the site of the fracture will be present. If a patient presents with ankle pain after an inversion injury, the Ottawa rules should be used

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to determine the need for imaging to look for a proximal fifth metatarsal injury.

Imaging

Standard AP, lateral, and oblique radiographs of the foot may be sufficient; however, tuberosity fractures can be missed on foot films, so it is also recommended to get ankle films as well [47]. Likewise, if a fracture is identified on ankle films, a dedicated foot series needs to be completed as well. CT or MRI should be considered in the setting of delayed healing or nonunion.

Management

Treatment depends on the fracture location and is subdivided into zone 1, zone 2, and zone 3 injuries. Zone 1 injuries are avulsion injuries that occur at the tuberosity. Zone 2 fractures occur at the metaphyseal-diaphyseal junction, while zone 3 fractures occur in the proximal diaphysis [48]. Zone 1 fractures occur in a well-vascularized region and heal without difficulty with conservative management. Treatment focuses on allowing patient to ambulate without pain. Treatment options include a hard-soled shoe, elastic dressing, or CAM walking boot for 4–6 weeks. Zone 2 injuries are also known as Jones fractures, and the concerns for malunion and nonunion are much higher than zone 1 injuries. Malunion and nonunion complications can occur with both operative and nonoperative management and is seen in approximately 20% with each [49]. Conservative management includes 6–8 weeks of non-weight bearing in a short leg cast; then if radiographic signs of healing are present, weight bearing can slowly be reintroduced [50]. Lack of radiographic healing at 12 weeks should raise concern for malunion, and the patient should be referred to orthopedics for discussion of operative management. For elite competitive athletes, initial treatment with surgical screw fixation followed by 6 weeks of non-weight bearing in a short leg cast is another option; however, this method does not remove the risk of malunion and nonunion. The treatment for zone 3 fractures is the same as zone 2; however, more prolonged immobilization may be required for chronic stress injuries that evolved into occult fractures. Total healing times of 18–24 weeks is not unheard of in this type of injury. As with zone 2 injuries, regular radiographic monitoring is needed to evaluate for healing complications.

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Part XIII

Common Clinical Problems

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Care of the Patient with Obesity

56

Birgit Khandalavala

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General Principles

Currently, there are relatively few therapeutic options that can be widely promulgated for long-term sustained weight loss, while at the same time, the rates of obesity are projected to escalate further [1–4]. These challenges make weight loss difficult for the patient with obesity. Three key points of care of the patient with obesity that the primary care provider should be aware of are:

1. The concept of obesity as a chronic disease with provision for multiple modalities of obesity therapies
2. The mitigation of obesity bias
3. Patient-centered health outcomes, rather than primarily weight loss goals

Epidemiology: Obesity is an increasingly prevalent condition in the United States (US) [5], leading the American Medical Association to declare obesity to be a disease in 2013 [6]. Currently, in the United States, the prevalence of overweight and obesity is over two thirds in adults

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and one third in children and adolescents [5]. Childhood obesity continues into adulthood for the 80% of children. By 2030, it is projected that more than half of the adult US population will have obesity and one in four American adults will have severe obesity, with the most likely impact in women, non-Hispanic black adults, and low-income adults [7]. Similar prevalence of obesity is projected for most of the world [8].

Definition and Classifications: Simply stated, obesity is a condition of excess body fat. Since the distribution of fat mass is difficult to determine in the clinic, the body mass index (BMI) was developed [9]. There are four categories of BMI: underweight (<18 kg/m^2), normal weight ($\geq$19–24.9 kg/m^2), overweight ($\geq$25–29.9 kg/m^2), and obese ($\geq$30 kg/m^2). BMI has prognostic importance and directly correlates to mortality risk. BMI should be considered a screening tool and is not diagnostic of obesity-related complications [3]. Electronic medical records calculate the BMI from available weight and height and for children 2–20 years of age; age- and sex-specific BMI percentiles are available [4].

The waist circumference (WC) is reflective of abdominal fat accumulation, with weight-independent cardiovascular risk implications. The guidelines recommend measuring a WC for patients with a BMI between 25 and 34.9 kg/m^2. A WC of over 40 in. in men and 35 in. in women meets the criteria for "obese" in Caucasians.

Etiology: Obesity is due to excess energy stored in the fat cells, which may be the result of a wide variety of causes [1–4]. There are a few rare purely monogenetic causes of obesity [4]. An early onset of obesity before the age of 2, family history, or the presence of other abnormalities may indicate Prader-Willi, leptin, POMC, or MC4R deficiency [4]. The current rational is that for a vast majority of the population, a genetic predisposition for weight gain, within a setting of an obesogenic environment, is causing excess energy production. Reduction of physical activity is aggravated as sedentary behavior becomes more the "new normal." Most of the genetic influences are polygenic and associated with a variety of genes of which the "Fat mass and obesity-associated (FTO) gene" is the most prevalent and is found in up to 43% of the population [10]. Epigenetic changes may result in lifelong metabolic changes [11]. Other factors implicated in the pathogenesis of obesity include weight-promoting medications, gut microbiome, sleep disturbance, endocrine disruptors, global warming, and food policies, among others. The biopsychosocial determinants of obesity are being increasingly recognized [12].

Physiological Control of Body Weight: A complex neurobiological regulatory process mediated by the hypothalamus in the brain, adipose tissue, and the gastrointestinal tract controls food intake and energy expenditure by secreting several hormones [13]. These hormones act to protect the body from weight loss, giving rise to the concept of a set point for body weight and "the thrifty gene." Human physiology is geared for weight gain and energy storage, and attempts at volitional weight loss will be counter-regulated by many physiological changes, as confirmed by energy studies in participants from the biggest loser reality shows [14, 15]. As a result, the patient's efforts to keep weight off are difficult, and weight regain typically occurs. A pivot away from personal blame and failure is occurring. Newer clinical competencies for providers in the management of obesity therefore stress the understanding of obesity as a complex disease and call for mitigating obesity bias [16, 17].

Effects of Weight Gain: Obesity impacts every organ system resulting in overall increased morbidity and mortality and correlates directly with increasing all-cause mortality [18]. The optimal BMI for longevity is in the range of 21–25 kg/m^2. Metabolic and cardiovascular diseases are the most common associations with obesity [19]. This may be independent of total mass or BMI especially in Asian ethnicities. Metabolic syndrome and insulin resistance with characteristic dyslipidemia and hypertension typically precede the onset of type 2 diabetes. Acanthosis nigricans, polycystic ovarian syndrome, nonalcoholic fatty liver disease, and gout are also common associations of metabolic syndrome. Type 2 diabetes and obesity are the most closely related, and a common condition of "diabesity" occurs in both adults and children

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[20]. Obesity is a common risk factor for hypertension, and concomitant sleep apnea can contribute to hypertension.

Cardiovascular risk is increased as a result of dyslipidemia, hypertension, diabetes, and sleep apnea. The cardiovascular complications associated with obesity are due to the increased subendothelial inflammation, insulin resistance, coronary calcification, and activation of coagulation, renin-angiotensin, or the sympathetic nervous system [21]. The metabolic syndrome pattern of dyslipidemia consists of elevated total cholesterol and significantly elevated triglycerides, with low HDL. Coronary heart disease, heart failure, atrial fibrillation, venous thromboembolism, and stroke are more frequent in patients with obesity and obesity-related cardiac risk factors.

Nonalcoholic fatty liver disease is rapidly becoming the foremost cause of liver disease and major indication for liver transplant in the future for complications of liver cirrhosis [22]. Female infertility, polycystic ovarian syndrome, and male hypogonadism can impact reproductive health [5].

While the cardiometabolic effects of obesity are well known, more recently a strong association with cancer and dementia is emerging [5, 23]. A correlation between obesity, enlarged waist circumference, and dementia is becoming clearer. With increasing BMI, the incidence of every type of cancer increases. These obesity-related cancers are predominantly reproductive, or in the GI system, however, even malignant melanoma has been seen to occur more frequently in patients with obesity, than in leaner patients. In women, breast cancer and uterine cancer are the most common, while in men colon cancer and prostate cancer are more common.

Due to the impact of pro-inflammatory cytokines and immunological aspects of obesity and increased baseline inflammatory status, patients with obesity may have reduced ability to fight infections, and patients with obesity are at increased risk of getting infections, with a reduced response to vaccinations, as has been seen with influenza and more recently with the coronavirus outbreak in 2020 [24].

The mechanical impact of weight gain and body size is seen to result in increased fat mass and causes osteoarthritis, sleep apnea and breathing problems, urinary incontinence, gastroesophageal reflux, and hernias. Orthopedic involvement of the hip in children can be a serious emergency. In adults, increased body pain with difficulty with physical functioning comprises the quality of life.

The psychological impacts of weight gain and mental health are closely aligned [3]. Depression often is present with weight gain, but obesity can also exacerbate underlying depression. Increased impulsivity traits occur at the observational and genetic epidemiology level [25]. Weight bias is highly prevalent and can be toward the patients by providers or even experienced by the patients toward themselves. Perception of weight bias is associated with diminished quality of life. Economic aspects of obesity include diminished earning capacity, increased disability, and lower income with overall increased mortality, while national costs of health care increase.

Management of the Patient with Obesity

Approach to the Patient: A patient-centric approach for the patient with obesity is to be encouraged. The five A's approach should be used: for the patient with obesity, the provider should "Ask Assess, Advise, Agree, and Assist (five A's)" [3].

Clinical Management

Screening: All children over the age of 6, adolescents, and adults are screened with BMI [26]. This is followed by assessment of obesity-related risk for the individual patients. Evaluation for secondary causes of obesity is not required, unless the initial workup is suggestive of an underlying endocrine or genetic cause. In children, greater vigilance for markers of an underlying genetic or endocrine abnormality is indicated. WC can be measured.

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History

First, the provider will obtain the patient's history of weight, nutrition, and physical activity, along with current medical, social, and family history. Additional information regarding the presence of comorbidities and complications is needed. All medication use, prescribed and over the counter, should be carefully noted and reviewed for obesogenic potential. Reproductive history in women will include menstrual periods, acne, and hirsutism. In children, monogenetic syndromes may be evident by severe and rapid growth in early childhood or family history. Urgent referral is indicated if hip pain is present in children as slipped upper femoral capital epiphysis is likely. A holistic assessment should also include sociocultural practices and beliefs, adverse childhood experiences, and psychological factors such as mood, anxiety, binge eating disorder, attention-deficit/hyperactivity disorder, self-worth, and identity [3].

Physical Exam

Weight and height are to be accurately measured. To facilitate correct blood pressure measurements, appropriately sized blood pressure cuffs should be available. Measuring the neck circumference is appropriate if the patient has untreated sleep apnea or elevated blood pressure. The physical examination should be complete and include evaluation for suspected secondary causes of obesity only if indicated. Establishing the presence of comorbidities of obesity that will need to be treated is critical. In children, a more detailed orthopedic and systemic examination is essential.

Laboratory Testing

The routine lab testing focuses on the determination of comorbidities and cardiovascular risk of obesity and includes cholesterol profile, fasting blood sugar, HbA1C, and liver enzymes. Routine insulin testing, detailed endocrine workup, and other evaluations for secondary causes are not routinely advocated. In children genetic testing may be indicated if severe obesity presents early, particularly if other features of syndromic presentation or family history are also present.

Treatment

Goals: Moderate weight loss of 5–10% is often seen to reduce risk factors and is the initial goal of treatment in the primary care clinic. More significant weight loss is possible, but long-term durability outside of bariatric surgery has yet to be clearly established. Maintaining the current weight of the patient and improved health and quality of life are often realistic goals for adults.

Guidelines: There are several guidelines available, consisting of multidisciplinary approaches to weight management: comprehensive lifestyle modification, pharmacology, and bariatric surgery options [1–4]. The 2016 AACE guidelines have replaced some of the focus on BMI. The latest, 2020 released Canadian guidelines stress improved health and quality of life, as opposed to a weight outcome, and contain a further shift away for BMI. The management of obesity in children now includes consideration of pharmacological agents and bariatric surgery. Weight loss in the elderly is controversial with no current guidelines. Preservation of muscle mass is a priority.

Comprehensive Lifestyle Modification. The USPSTF recommends referral of all patients with obesity to a comprehensive program [26]. The components of any comprehensive program include diet, physical activity, and behavior modification [1]. The long-term efficacy of such programs is limited to about 3–5% long-term weight loss. There could be other benefits besides weight loss, and there are minimal side effects to healthier eating and increasing physical activity.

Diet

Dietary changes are mainly focused on weight reduction by producing an energy deficit. These can be an overall caloric restriction diet such as

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low calorie or one macronutrient as in the low-fat diet and low-carbohydrate diet. Other diets that increase proteins or ketones are popular. The most recent diet studies indicate that all diets seem to work about the same, for short periods of 3 to 6 months, with equal efficacy. Fasting and timed eating are becoming trendy, but evidence of effectiveness is currently not available. What is clearly established is that adherence to a preferred diet by the patient may be more critical. A healthy eating pattern consists of increasing the amount of nutrient-dense foods from all food groups and limiting the intake of empty calories from added sugars and saturated fat, with reduction of sodium intake [27].

Physical Activity

Both voluntary exercise and activity as part of daily living that requires the usage of energy are important for health. Physical activity directly helps avoidance of weight regain and has significant benefits that may not be weight related. The current guidelines recommend 150 min a week and twice weekly weight or resistance training; however even small amounts of physical activity may be advisable. Aerobic activity of 30–60 min on most days of the week can lead to small amount of weight loss and help keeping weight off. Physical activity reduces all-cause mortality, and for most healthy people these goals are possible, without too much effort [28].

Behavioral Management

Multicomponent psychological interventions are moderately effective, and evidence suggests that intensive, multicomponent behavioral interventions with 12 to 26 sessions per year are the most effective. Interventions proven to be effective include motivational interviewing, self-monitoring, goal setting, stress reduction, and cognitive restructuring. Group activities or in-person modalities may lead to better outcomes than those that rely only on online delivery to an individual.

Pharmacological Management of Obesity

The use of medications for weight loss is indicated for patients with a BMI of $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with adiposity-related complications, as an adjunct to lifestyle therapy, and not alone [1]. There are very few medications available for long-term use, and many of the weight loss medications have been removed from the market, over the years, due to the side effects and safety concerns. The use of medications for 3 to 6 months of time is not recommended [1]. Prior to prescribing any weight loss medication, a review of the current list of medications of the patient should be undertaken to see if any changes and substitutions can be made to any weight-inducing medication. The efficacy of the FDA-approved medications has ranged from 3.9% weight loss for orlistat to 7.8% 1-year weight loss for liraglutide. All weight loss medications are contraindicated in pregnancy [1].

The older sympathomimetic medications were approved for short-term use for 12 weeks. Due to the mechanism of action, they have many adverse side effects as a result and include increases in blood pressure and heart rate insomnia and potential abuse. Phentermine is the most common medication used for obesity. More recently an 8 mg dosage is available for dosing three times a day.

The pancreatic lipase inhibitor orlistat has been available for a number of years as prescription and, for adults and children 12 years and older, and is given as 120 mg three times a day before meals. A lower dose of 60 mg has been available over the counter. Results are limited with average weight loss below 3% maintained over time. The medication is given orally, blocks the absorption of fat from the intestine, and has demonstrated metabolic benefits in delaying the outcome of diabetes and lipid profile, but use is limited due to significant gastrointestinal side effects of cramping, flatus, and fecal incontinence.

In 2012, a combination of phentermine and topiramate involved two previously approved FDA medications, reformulated into one new FDA weight loss medication. The side effects include those of phentermine with the addition

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of those from topiramate which consist of paresthesia, dysgeusia, cognitive changes, glaucoma, and potential for fetal toxicity. Cardiovascular risk was evaluated in two studies and was found to be favorable; however, the cost and the side effect profile have limited widespread usage.

The combination of naltrexone and bupropion into a single weight loss medication similarly includes two previously approved medications that were reformulated and subsequently approved by the FDA for long-term weight loss. Hence, the side effects consist of those from both medications. While bupropion is familiar to most primary care providers as an antidepressant, with side effects of blood pressure and heart rate elevation and lower seizure threshold, naltrexone can cause nausea and cannot be given to patients on opioids. Warnings include suicidal behavior and ideation, and contraindications include uncontrolled hypertension, seizure disorder, bulimia or anorexia nervosa, chronic use of opioid drugs, abrupt discontinuation of alcohol, and MAOI use.

Lorcaserin acts on the serotonin receptors in the brain, and helps with satiety, but has the potential of interacting with other medications affecting serotonin to produce the serotonin syndrome. Dosage is 10 mg twice a day, and the medications are well tolerated with mild side effects that include constipation, cough, dizziness, and tiredness. However, lorcaserin has been withdrawn from the market in February 2020 due to cancer potential.

Liraglutide is a long-acting glucagon-like polypeptide receptor agonist that is injected once a week, at a dosage of 3 mg. The medication is used widely for diabetes in primary care, at a lower dosage of 1.8 mg, and found to have cardiovascular benefits [29]. The most common side effects associated with liraglutide 3 mg are gastrointestinal and include nausea, diarrhea, vomiting, and constipation with warnings of pancreatitis, acute cholelithiasis, and cholecystitis. Liraglutide has been reported to cause thyroid C-cell tumors in rats, and so far not in any humans, but the drug is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or with multiple endocrine neoplasia. Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide.

Emerging obesity medications include semaglutide and multiple treatment options with monotherapy or combinations of various hormones (GLP-1, GIP, glucagon, oxyntomodulin, amylin, PYY). No supplements or over-the-counter medications have been found to be useful, despite many claims on the Internet, social media, or by individual patients.

Surgical Management of Obesity

Bariatric surgery is indicated for patients with BMI over 40 or 35 with obesity-related comorbid conditions and is the most durable and effective modality for treating obesity and obesity-related complications [30]. The number of procedures has been seen to increase since results of bariatric surgery have consistently shown reduction in the weight and in type 2 diabetes. Bariatric procedures are restrictive, malabsorptive, or mixed of which the gastric sleeve and gastric bypass remain the most popular. The long-term outcomes following bariatric surgery are on average 7-year mean weight loss of 28.4% for the gastric bypass. The prevalence of dyslipidemia, diabetes, hypertension, and remission of diabetes at 7 years was 60.2% for Roux-en-Y gastric bypass and 20.3% for laparoscopic adjustable gastric banding [31].

Laparoscopic adjustable gastric band was the most commonly performed restrictive surgery with a tight adjustable band placed around the top of the stomach and an infusion port to allow for adjustments. The number of procedures for the band has been declining due to side effects and limited weight loss after 2 years.

Laparoscopic sleeve gastrectomy is a single-stage restrictive surgery where about 85% of the stomach is removed and a tube or “sleeve” is made of the remaining stomach. This is becoming the more common with durability of about 5 to 9 years. GERD symptoms may worsen in those patients with the sleeve, and weight loss is not as maintained as with the gastric bypass, with some

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patients requiring reoperations for severe GERD. Since there is minimal malabsorption, vitamin and protein deficiencies are relatively rare.

The Roux-en-Y gastric bypass consists of two stages: the first part consists of cutting the stomach into a small gold ball-sized upper pouch which is separated from the rest of the stomach, and the second part consists of the attachment or bypass of the remaining part of the stomach and intestine, by pulling up a loop of the jejunum and attaching it to the pouch of the proximal stomach. Due to the restrictive and malabsorptive parts of the procedure, the complications can consist of leaks, hernias, and other surgical complications, in addition to the need for lifelong supplementation of vitamins and often iron and protein.

Prevention: Once excess weight is gained, options for the management of weight loss are limited by physiological counter-regulation as well as continued exposure to the obesogenic environment. Prevention of any further weight gain is critical. A multidimensional approach as laid out by the AACE model will take decades to implement [1]. In the meantime, obesity rates are only going to increase; for family medicine providers, a focus on pregnancy weight gain optimizations, childhood weight management, and aggressive management of adult obesity-related comorbidities may be the most strategic responses in the interim.

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Care of the Challenging Patient

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Mark Ryan

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General Principles

Definition/Background

Although the chapter title and some of the references included here will use the phrases "difficult patient" or "frustrating patient" – or even "hateful patient" – it should be made clear that this is not the author's preferred term. Any doctor/patient interaction by definition involves at least two parties, both of whom have personalities, preconceptions, and prior experiences that are incorporated into current interactions. Difficulties in physician/patient interactions also incorporate patient, physician, and healthcare system factors [1]. For these reasons, phrases such as difficult or challenging patient interactions are preferred.

Epidemiology

Family medicine physicians in the United States account for more than 214 million office visits yearly [2], and 15–37% of physicians' patients can be described as frustrating or difficult [3, 4]. It is clear, then, that in any given year, family physicians will encounter a large number of patients with whom they will have difficult, frustrating, or challenging interactions.

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Approach to the Patient

To discuss difficult patient interactions, it is important to first discuss the characteristics of a therapeutic doctor/patient relationship. According to the AMA's *Journal of Ethics*, "a patient-physician relationship is generally formed when a physician affirmatively acts in a patient's case by examining, diagnosing, treating or agreeing to do so" [5]. Once a physician agrees to take on this role, the physician then owes that patient a duty to continue to treat them or to properly end the relationship [6]. Physicians are expected to provide their expertise via their sapiential authority (their medical training and competence), their moral authority (their concern for and obligation to the patient), and their charismatic/empathic authority (their emotional connection and care for their patients) [7]. Physicians must approach patients with inclusion, characterized by personal engagement, and availability, an openness to learn about others' experiences [8].

From the patient perspective, patients want physicians to help orient them to visits, to assess their understanding and preferences, and to engage in meaningful discussions [9]. Patients identified physician communication, respect for the patient, sympathy, empathy, patient-centeredness, and shared decision-making as important elements they sought in doctor/patient interactions [10].

Effective doctor/patient relationships, in turn, result in improved trust, commitment, and adherence to care recommendations [11], and effective relationships result in improved healthcare outcomes including biomedical markers, behavioral outcomes, and improved communication between physicians and patients [12, 13].

Although "difficult patients" will differ in their specifics, there are common characteristics. "Frustrating patients" report higher rates of somatic symptoms, rate their own health status poorly, and are more often diagnosed with somatization or generalized anxiety disorder than "satisfying" or "typical" patients, even though those patients' physicians did not identify any differences in the severity of underlying health issues [3]. Patients who were described as "difficult" are also more likely to screen positive for mental illness and to be diagnosed with specific psychiatric disorders such as multisomatoform disorders, generalized anxiety or panic disorder, dysthymia or depression, and alcohol dependence. "Difficult" patients were more likely to list a larger number of active symptoms and to be diagnosed with functional illnesses such as irritable bowel or fibromyalgia while not showing any difference in "organic" illnesses such as diabetes, hypertension, cardiac disease, etc. "Difficult" patients were also more likely to report higher levels of impairment or disability than "not-difficult" patients [4]. Patients who were part of difficult encounters demonstrated lower functional status. Increased numbers of patient concerns, symptoms, or symptom severity were more likely to result in a patient being described as "difficult" [14].

Family medicine physicians have identified difficult patients as those who have behavioral problems (violent, aggressive, rude, lying, demanding, exploitative), patients who present with repetitive symptoms that never improve or who have multiple complaints, and those patients with psychiatric illnesses [15]. Physicians have further identified patient behaviors that characterize difficult encounters, including insisting on an unnecessary medication, showing dissatisfaction with care provided, etc. [16]. In one study in a resident clinic, poor social support on the part of patients was also associated with problematic doctor/patient relationships [17]. A recent qualitative study explored the ways in which patients who have experienced social inequalities may be considered to be "difficult" because of the demands physicians may feel to address serious health issues in the face of social needs. The increased time required to care for these patients and the frequent feeling of ineffectiveness in being unable to address root causes of patients' problems further complicate these patient encounters [18]. Physicians were also more likely to report difficult patient encounters when patient behaviors and medical problems were opposed to physicians' personalities and approaches to care [19]. Finally, challenging patient interactions may impact physicians' diagnostic accuracy [20], which may risk additional harm to the patients involved.

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Diagnosis

In 1978, Groves identified four types of "difficult" (or, as described in the article, "hateful") patients and characterized them as noted below [21]. Although the language is inappropriate in today's patient-centered approach to care, a reevaluation of this model updated for the twenty-first century [22] highlights the fact that these four general categories are still relevant today and may serve as archetypes to facilitate initial approaches to caring for these patients. The update notes that illness and disease can be considered a direct threat to the patient's integrity, and this threat causes individuals to turn to behaviors or coping mechanisms that may not be beneficial or effective.

- Dependent "clingers": characterized by "repeated, perfervid, incarcerating cries" for care and reassurance and "their self-perception of bottomless need and their perception of the physician as inexhaustible" which lead to fatigue and frustration.
- Entitled "demanders": "use intimidation, devaluation, and guilt-induction to place the doctor in the role of the inexhaustible supply depot," but this approach generates from a concern for abandonment and "an effort to preserve the integrity of the self" when confronted by illness or potential harm.
- Manipulative "help rejecters": need significant amounts of physician attention, but rather than expecting or demanding to get better, they appear to doubt that any care offered will make a difference, and if one symptom is resolved, other symptoms are likely to replace it. These patients are described as having a "need/fear dilemma"; they have needs that they seek to address, but fear either being abandoned or overwhelmed. This was clarified in 2006 [22] by noting that in this case patient's goal is the relationship with the physician as opposed to a cure.
- Self-destructive "deniers": these patients are described as continuing behaviors that actively contradict or undercut physicians' attempts to help them and have "given up hope of ever having needs met."

In a small study, Schafer and Nowlis noted that patients described as difficult by physicians were more likely having personality disorders than control patients and that physicians were often unaware of these diagnoses [23]. The four categories of difficult patients listed above parallel definitions and diagnoses of personality disorders, especially those in clusters B and C. Given the fact that personality disorders are enduring, pervasive, and inflexible [24], patients with these characteristics will likely demonstrate persistent challenges in physician/patient interactions and will tend to use those approaches with each healthcare visit – allowing identification, categorization, and approaches to care as described later.

Levinson et al. categorized seven specific patient-driven themes/frustrations that contribute to difficult interactions:

1. Lack of trust or agreement
2. Lack of adherence to recommended plans of care
3. Too many problems, especially when combined with a lack of adequate time to address each of them
4. Feeling distressed (angry, overwhelmed, etc.) after office visits
5. Demanding or controlling patients/families (different from patient-centered care and the idea of shared decision-making)
6. Lack of understanding due to the use of medical jargon or lack of language proficiency
7. Specific problems that are difficult to address, such as substance abuse, chronic pain, etc. [25]

It is notable that each of these categories of frustrations does not result from a unilateral patient-side fault. There is a bilateral obligation on the part of patients and physicians to ensure proper and meaningful communication as part of the visit, and to make shared decision-making is a focus of each visit.

While considerations of personality disorders and psychopathology are important, we must also consider patients' prior experiences with the healthcare system, especially in cases where patients may have experienced active discrimination or where they have felt that their concerns have not been taken seriously. One study

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demonstrated the prevalence of discriminatory behaviors which patients who are members of sexual and gender minority groups included in but limited by the LGBTQ communities [26]. In other cases, patients' race or ethnicity has resulted in their medical needs being disregarded [27]. Negative past experiences with healthcare systems and healthcare providers may predispose patients to a more assertive or a more distrustful presentation, which may lead to labeling a patient as "difficult" and cause challenging interactions. Compared to personality disorders or more pervasive patient traits, however, these interactions may be improved once the patient has trust in their current physician and physicians have proven that they can be trusted.

Physician characteristics such as age, ethnicity, and number of years in practice have not consistently been associated with an increase likelihood of experiencing difficult doctor/patient interactions. However, physicians with poorer psychosocial attitudes were more likely to experience difficult patient encounters, and communication defined as "psychosocial" (as opposed to biomedical) was more likely to be associated with patient and physician satisfaction [14]. Physicians working in health maintenance organizations (HMOs) as opposed to private practice, as well as primary care physicians, have indicated higher levels of frustration [25]. Although fewer physicians work in HMOs than in the late twentieth century, this observation is still important and could carry over to physicians working as health system employees and who face similar administrative pressures and lower levels of personal control over their practice than would be the case in private practice. Physicians who reported a high frequency of difficult interactions were more likely to report feeling burned out and less likely to be satisfied with their jobs [16]. In a study that evaluated the characteristics of physicians who worked with "heartsink" patients – patients who created a sense of impotence or helplessness in their physicians – it was noted that physicians were more likely to report they worked with "heartsink" patients if they had "more than the usual workload" [28]. Finally, younger physicians, those who work longer hours, and those physicians whose patient panels include high numbers of those with substance abuse or challenging psychosocial backgrounds were more likely to report that they had a high number of "difficult" patients [29].

In addition to physicians' own assessment of issues that are likely to increase the risk of difficult patient interactions, patients have identified that they have lower trust in their physicians if their physician is not answering questions in ways that they can understand, if physicians are not taking time to answer questions, or if physicians are not giving enough medical information [30]. This lower level of trust made patients consider changing physicians and would likely present a risk for difficult or challenging doctor/patient encounters: if therapeutic relationships are at the heart of the work done by family physicians, then any experience or perception that reduces trust in that physician will interfere with this core principle.

The relationship between a high number of difficult patient interactions and reported high stress/low job satisfaction seems evident, but it is difficult to separate cause from result. Physicians working with large numbers of "heartsink" patients may report increased burnout, but that burnout may predispose physicians to more challenging interactions.

Difficult physician/patient interactions are not solely due to physicians or patients. Rather, they result from interplay of different elements. These elements include patient and physician factors as described above, but other elements must also be considered [31]. The illness itself and the health system in which patients access care play important roles in the creation of a difficult interaction. Difficult relationships may occur when physicians and/or patients do not feel that interventions are successful or effective; when patients/physicians are not flexible or adaptable in terms of addressing diversity of thought, experiences, or preferences; or when patients/physicians have misaligned expectations about goals and anticipated outcomes of care [32].

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Treatment

In family medicine, it is important to consider that a patient's illness can be defined by predisposing factors, precipitating factors, and perpetuating factors [33]. This model may be used to consider how to approach a difficult physician/patient interaction. The predisposing factors would include the patient and physician factors listed earlier; the precipitating factors may be a particularly difficult interaction, a sudden stress experienced by the patient, or puzzling symptom that is hard to explain; and the perpetuating factors would be a lack of trust, poor communication between the parties, or mismatched goals of care. With this in mind, we need to consider what can be done to address predisposing factors in advance of the visit, how to recognize a precipitating factor when one occurs and how to limit the precipitating factors we can control, and how to reflect after a visit on what factors might be perpetuating the problem. This last step includes how to ensure physicians are taking care of themselves in order to sustain the resilience needed to work with challenging patients.

Before the visit: Virtue ethics describe individual traits which "dispose an individual to act justly in a particular situation," and the ethical values of courage and compassion may be especially important in working with challenging patients, given that these patients may test physicians' abilities to stay engaged with them over time and to continue to feel empathy in the face of an often-difficult relationship [34]. Strong physician job satisfaction, appropriate physician workload, and training in communication skills and in counseling are associated with a reduction in physician perceptions of patients as being difficult or frustrating, while working with complicated patients with multiple medical problems or in time-restricted settings increases physician frustrations. Postgraduate training in communication and point-of-care counseling interventions, reduced number of patients seen by physicians, and/or increased time provided for patient visits may be beneficial. Training in active listening [35] may help physicians better care for patients by incorporating patients' concerns into encounters. Encouraging ongoing doctor/patient relationships allows a stable dyad to address various ongoing medical issues without feeling obligated to address all of them at any one time.

Enhanced training and education of individual physicians can address some of these issues, but others will require reevaluation of the current practice environment. Fee-for-service payment models result in family physicians being encouraged to see more patients in any given amount of time and are at risk of perpetuating those factors that physicians have identified as making patient interactions more difficult. In comparison, models of patient care such as patient-centered medical homes or direct primary care may allow for lower volumes of care and longer visits for complicated patients and may increase job satisfaction and physician perception of control. These factors, in turn, may help enhance physician resilience and reduce the frequency of challenging or frustrating interactions. Addressing time pressures and encouraging physicians and patients to talk about concerns and shared approaches to diagnosis, evaluation, and treatment will improve patient experiences and help reduce the level of frustration felt within the relationship.

Strong patient/physician relationships, which include both a physician's empathy toward the patient and patient empathy toward the physician, may help avoid challenging interactions by improving understanding on both sides of the dyad. Graphic medicine has been proposed as a potential tool to facilitate co-learning between patients and physicians [36] to allow each to better understand the concerns and context experiences by the other.

In the exam room: During office visits with frustrating or difficult patients, there are useful approaches to identifying which patients may need more attention and to working effectively with patients who generally present challenges to the physician. It has been suggested that a physician's own frustration with a patient might be a marker for which patients may benefit from

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mental health evaluation and care and that using Kleinman's explanatory model [37] may help enhance communication between physician and patient [3], especially if there are discordant views of the patient's health status.

Carde suggested approaches to working with patients defined as "difficult" as a result of their social circumstances. The recommended steps include building a good relationship with patients who may have been marginalized in the past, being realistic about what care can be provided and how much progress in providing care might occur in any given encounter, and interacting with colleagues who share this work – as a way to both decompress the stress which might result from the encounter and share best practices and learn new ways to work with these patients [18]. These suggestions are broadly applicable to any challenging patient, especially if social stigma, discrimination, or injustice may be part of their histories.

Active listening, an approach in which physicians move beyond facilitation skills to become aware of cues in patients' comments or behaviors that suggest underlying concerns, may help physicians better elicit the patient's perspective on their illness. Patients may present their perspective via direct statements, expressions of feelings, or concerns about an illness, repeating certain ideas or concerns about an illness, or behaviors such as reluctance to accept recommendations, interrupting the physician, "by the way" statements as a visit closes, etc. [35]. By recognizing these cues, physicians can seek to better understand patient concerns they may not have fully addressed and will be able to refocus their energy in those areas as well as rephrase their conversations with patients to encourage further discussion and disclosure.

Providing patients with diagnoses, prognostic information, etc. is associated with fewer ongoing concerns or continued symptoms and with improvement in symptoms after medical visits, and "difficult" patients were less likely to have received such information and more likely to describe unmet expectations [38]. This suggests that using the patient's explanatory model to frame the discussion of a patient's illness (including functional illnesses) may help align a physician's diagnosis and plan of care with a patient's expectations from a given office visit. Enhanced diagnosis and treatment of mental illness, increased psychosocial awareness and improved communication on the part of physicians, and standardized approaches to manage somatization may help reduce the difficulty of physician/patient interactions [14].

Building out of the four "hateful" patients he described [21], Groves suggested approaches for caring for difficult patients, including setting firm guidelines to doctor/patient interactions, refocusing patients' demands for any and all available interventions or evaluations toward those that will actually provide benefits, noting that treatment may not be curative but that it may help address symptoms, and working to provide the best care possible under the circumstances. In each of these situations, it is important to ensure that specific underlying issues of mental illness have been considered and evaluated while recognizing that a lack of insight on the part of the patient might limit the effectiveness of such evaluations and interventions. Personality disorders are best approached with techniques such as motivational interviewing and shared problem-solving with the patient [24]. Physicians can approach "difficult" patients using empathy to try and understand the patient's concerns and circumstances, listening with patience and without judgment, setting clear guidelines for patient encounters, and using referrals and specialists judiciously and appropriately [15].

Should a physician notice there is tension or discomfort in a patient interaction, it is important to assess what has happened and to consider the appropriate approach to remedy the situation. This process includes recognizing and acknowledging that tension has developed, assessing the source and the nature of the difficulty, and using a problem-solving approach that aims to preserve the relationship as well as addressing the medical needs while not losing sight of compassion or the importance of appropriate boundaries [32]. This stepwise approach may help avoid conflict and tension and may minimize the experience of difficult interactions between patients and physicians.

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One approach to difficult clinical encounters summarizes many of these considerations. The CALMER approach (Table 1) provides six steps family physicians can use during difficult patient interactions and focuses on physician responses to difficult encounters while seeing to preserve the relationship [39]. Experienced physicians have also noted that challenging medical encounters could be salvaged (or encouraged) through physician/patient collaboration and the appropriate use of power and empathy in the encounter [19].

McCarthy et al. suggested a different, more concise approach to working with difficult patient encounters, which they compare to the SOAP model often used in medical visits (Table 2).

After the visit and physician self-care: Mindfulness techniques can be an important aspect of addressing difficult clinical encounters. Relatively simple interventions such as centered breathing techniques or reflection on important events at the end of a clinic day are easily put into action [41].

Table 1 The CALMER approach

C: Catalyst for change	Identify where patients are in the stages of change model, and assess their readiness to advance to the next stage
A: Alter thoughts to change feelings	Identify the thoughts patients generate, remember not to take anything personally, and consider how to move forward without feeling angry
L: Listen and then make a diagnosis	Listen to patients, and watch for nonverbal cues in order to accurately interpret information before making a diagnosis/decision
M: Make an agreement	Share decision-making with the patient
E: Education and follow-up	Work on a treatment plan the patient has agreed to, provide information to make it successful, and then plan the next visit
R: Reach out and discuss feelings	Following the visit, reflect by yourself and with others regarding the events and the encounter

Pomm et al. [39]

Table 2 ROAR

Reflective	Validate patients' concerns, and help them open to the encounter
Objective	Encourage patients to share their histories and share their clinical data with them
Assessment	List what is known and what is still under investigation; emphasize the process involved in making a diagnosis
Reassurance	Ensure patients know you are available for questions and follow-up care

McCarthy et al. [40]

An important element of working with patients is empathy, in which physicians attempt to understand to identify with another person's situation. Empathy can enhance a physician's flexibility, ability to work within a patient's frame of reference and to maintain a professional relationship without developing negative reactions to difficult interactions. "[T]hrough patience and tolerance, the physician may get a sense of where the patient is coming from and why the patient has resorted to negative response patterns." Empathy can be fostered by recognizing one's emotions in the moment of an event, reflecting on negative emotions in themselves and in their patients, focusing on the emotional content in patients' histories, being aware of patients' behaviors and nonverbal cues to encourage and enhance communication, and accepting patients' feedback (even if it is negative feedback) as a way to improve their performance while allowing the patient to open up about their concerns and worries [42].

Physicians must also be aware of the risk of countertransference, in which they may develop feelings toward patients based on the physician's own prior experiences and life circumstances. Just as patients engage in transference (where they project experiences from their lives onto the doctor/patient interaction), physicians may project onto patients via countertransference and must be mindful of this reaction and of the patient factors that trigger it [22].

Balint groups have been suggested as a way to help physicians sustain their engagement with patients with whom they may have difficult interactions or relationships. The work of Michael and Enid Balint defined what a therapeutic

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relationship should look like: a shared commitment to investigating ultimate causes of both the current illnesses and the patients' reaction to them, as well as the importance of taking the whole picture into account and acknowledging the patient's concerns as a key element of the illness and the physician's role in helping the patient move forward [43]. The goal of Balint groups is to evaluate difficult patient interactions and encounters and to help physicians reach a deeper understanding of the patient's perspective of the illness, the relationship, and the current situation. Balint groups for general practitioners have been effective in enhancing physicians' sense of competence in working with patients and in better understanding difficult relationships, in strengthening professional identity, in helping identify skills used in the group that are also effective in patient encounters (active listening, etc.), and in promoting endurance and satisfaction [44]. Balint groups may be important tools in enhancing physician effectiveness and caring, avoiding burnout, and improving professional satisfaction.

Another approach to assess individual performance after difficult encounters is through use of a Critical Practice Audit. As presented by Stephen Brookfield [45], the Critical Practice Audit allows physicians to consider critical events in a preceding week, assumptions they made (and that patients may have made) that contributed to the situation being challenging, what other perspectives should have been considered during the event, and how a situation may have been handled differently.

The importance of preparing for challenging patient encounters before the office visit and in reflecting and evaluating the outcomes after the visit has been evaluated by using the BREATHE OUT process. BREATHE OUT is a brief tool that involves physician and team preparation before difficult patients are seen in clinic and provides for a structured, reflective review following the encounter (Table 3). In a randomized trial, using BREATHE OUT improved physician satisfaction with challenging patient visits [46].

Finally, other interventions that can be pursued outside of the clinic include familiarizing oneself with community resources, scheduling patients appropriately to allow longer time for more complicated patients, and ensuring continuity of care [1].

Table 3 BREATHE OUT

Before the encounter	
B	List at least one **b**ias/assumption that you have about this patient
R **E**	**Re**flect upon why you identify this patient as "difficult"
A	List one thing you would like to **a**ccomplish today
T **H**	**Th**ink about one question you'd like to address today that would enable you to further explore your assumptions, including a patient-centered social history review
E	Stop before you **e**nter the patient room, and take three deep breaths in through your nose and out through your mouth
After the encounter	
O	Reflect on the **o**utcome of the encounter. From the patient's perspective, what was their agenda? From the physician perspective, did you accomplish your agenda?
U	Did you learn anything **u**nexpected?
T	List one thing you look forward to addressing if you were to run into this patient **t**omorrow

Family and Community Issues

While patients described as "difficult" demonstrated increased use of healthcare services [4], Grove suggested that difficult patient interactions could risk harm to patients by fracturing the necessary therapeutic doctor/patient relationship via inappropriate confrontation with the patient or attempts to avoid or exclude patients from the healthcare system [21]. Using the 10-item version of Difficult Doctor-Patient Relationship Questionnaire (DDPRQ-10), physicians reported difficult patients to be frustrating, time-consuming, and manipulative and reported that they felt communication was difficult and were ill at ease and lacked enthusiasm for caring for these patients in the future [4]. Given the definition of a therapeutic doctor/patient relationship, it is clear to see that when patients are identified as challenging, it will be more difficult for their physicians to form effective relationships with

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them. "Difficult" patients are also less likely to be satisfied with their healthcare and to seek more medical visits and interventions [14], suggesting that finding effective ways to work with challenging patients can lower healthcare utilization and prevent complications associated with healthcare. Physicians reporting a high number of difficult interactions were also more likely to indicate that they had engaged in suboptimal patient care practices in the past year and more likely to expect future errors in their practice [16]. Though this trend did not reach statistical significance in the study cited, it does raise the concern that a physician facing a high number of difficult patient interactions could cause inadvertent harm despite best intentions.

Closing

The nature of medical care, especially family medicine, is that we will see many patients and we will all face patient encounters that are difficult and challenging. By being aware of patient factors that increase the risk of these interactions and physician and system factors that may precipitate or perpetuate challenging relationships, family physicians can take active roles in our patients' healing while also enhancing our own skills in working in these difficult circumstances and working toward the goal of changing systems to benefit our patients.

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Care of the Patient with Fatigue

58

Sarah Louie

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General Principles

Background

Fatigue is a common complaint in the primary care setting, with reported prevalence ranging from 5% to 10% [1]. With such a broad differential to consider, determining the cause of fatigue and helping the patient to find the appropriate

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treatment can be a daunting task. Similarly, chronic fatigue syndrome (CFS), a syndrome which arises in the setting of numerous biological, psychological, and social factors, can pose a diagnostic and treatment dilemma for the family physician.

Although fatigue has been described since the beginning of written history, it was not until 1896 that Beard first coined the term *neurasthenia*, a condition resulting from the depletion of the energy of the central nervous system [2]. Over time, various terms have been used to describe similar illnesses, with various etiologies proposed, ranging from environmental changes associated with modern living to immunological and postinfectious, including Epstein-Barr virus infection [2]. Fatigue in most patients is multifactorial, and the diagnosis of chronic fatigue syndrome is one of exclusion. It is thought to arise from a combination of genetic, neurological, immunological, and social factors, without one specific etiology. In this chapter, the evaluation of fatigue will be reviewed as well as the approach to diagnosis and treatment for CFS.

Epidemiology

While fatigue is a commonly reported symptom in the primary care setting, CFS is far less common. The prevalence of CFS has been noted to be similar across many different cultures and countries but does vary between studies. Epidemiological studies of two US cities demonstrated rates between 0.23% and 0.42% [2, 3]. CFS is more common in adults than children and more common in women and minorities [3]. Special considerations for diagnosis and treatment of CFS in these populations are discussed later in this chapter.

Approach to the Patient

Diagnosis

The differential diagnosis of fatigue encompasses many medical and psychiatric conditions including metabolic, infectious, sleep disorders, depression, and malignancy, just to name a few. When fatigue is present for more than 6 months and no laboratory or physical abnormalities are found, the diagnosis of CFS can be considered.

The diagnosis of CFS can be a difficult one to determine, and many diagnostic criteria have been proposed to aid both treatment of patients and research. In 2015, at the request of several governing bodies including the Centers for Disease Control, the Institute of Medicine proposed new diagnostic criteria for CFS to facilitate a timelier diagnosis and treatment as well as improve healthcare provider and researcher understanding of the disease [4]. In addition to this, they published a guidebook for clinicians which is very helpful, if detailed review of this syndrome is available online. In the criteria outlined in Fig. 1, the duration of 6 months or more is important, because it distinguishes CFS

Must have the following three symptoms:

1. Substantial Reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities
    a. persists **more than 6 months**
    b. accompanied by fatigue that is
        i. often profound
        ii. New or definite onset
        iii. Not the result of ongoing excessive exertion
        iv. Not substantially alleviated by rest
2. Post exertional malaise
3. Unrefreshing sleep

AND at least one of the following:

1. Cognitive Impairment
2. Orthostatic Intolerance

Fig. 1 IOM diagnostic criteria for CFS (SEID) [4]

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from other causes of fatigue. In their report, it is also proposed that the name for CFS be changed to systemic exercise intolerance disease (SEID) to focus on the central characteristic of the syndrome which is that exertion of any sort (physical, cognitive, emotion) adversely affect patients in multiple organ systems [4]. The need for ongoing monitoring for those who do not meet criteria as well as comorbidities in those who do is also important [4].

History

In addition to assessing for the above symptoms, a detailed history should focus on the time course of the fatigue, the patient's social history including drug and alcohol use, and current use of medications and supplements [5]. It is also important to consider the medical and psychosocial context within which the fatigue developed as well as prior history of trauma, including adverse childhood events (ACEs) and the social support system of the patient [6]. These components of the history are important, not only for making an initial diagnosis but also for designing a treatment plan tailored to the patient's individual needs and available resources.

Physical Examination

Physical examination of the patient with fatigue should be focused on assessing for underlying infection, inflammatory conditions, and metabolic disorders in addition to gaining an overall sense of the patient's well-being and function.

Laboratory Testing and Imaging

When evaluating the cause of fatigue, prior to considering CFS as the potential diagnosis, it is important to first look for other underlying causes of fatigue. Not all tests listed in this chapter are indicated for all patients. Laboratory testing should be directed at the patient's symptoms and clinical presentation. For example, testing for viral or bacterial infections is not indicated unless the history and/or physical exam indicates an infection may be present [7] (Fig. 2).

If the above indicated laboratory testing is within normal limits and no other underlying medical or psychiatric conditions can explain the patient's fatigue, the diagnosis of CFS should be considered based on the diagnostic criteria mentioned above.

Treatment

Patient perception lies at the heart of treatment of CFS. Predictors of improvement in symptoms were not related to disease severity or chronicity of the patient's fatigue in one British study but rather the patient's attitudes and beliefs surrounding the illness [8]. For example, patients who participated in support groups had a lower

Complete blood count with differential
Basic Metabolic Panel
Calcium
Phosphorous
Liver function tests (including AST, ALT and alkaline phosphatase)
Albumin
Total Protein
ANA
Rheumatoid factor
TSH and Free T4
Ferritin (especially in children and adolescents)
UA for protein, blood and glucose
Testing for gluten sensitivity
Sleep study

Fig. 2 Tests to consider when evaluating underlying causes of fatigue [5, 7]

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treatment response than those who did not, largely because the group patients tended to participate in reinforced certain illness beliefs as well as exercise avoidance [8]. The two treatments for CFS with the best evidence are cognitive behavioral therapy (CBT) and graded exercise therapy (GET). Both are thought to have an impact on the patient's beliefs about fatigue and their own limitations secondary to their fatigue. A change in patient beliefs surrounding fatigue as well as improving patient's sense of empowerment and self-efficacy whether by CBT or GET is likely to be beneficial for a patient CFS.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) has been demonstrated in several studies as more effective than usual care or other psychological treatments including relaxation, counseling, and relaxation/support, though the data on the long-term effects of this are inconclusive [8]. More research is needed into whether CBT or CBT in combination with other therapies such as graded exercise is most optimal, as well as the acceptability of CBT among patients with CFS [8]. Given its demonstrated benefit, at least in the short term, it would be reasonable to offer CBT as a treatment modality to a patient with CFS regardless of the duration or severity of symptoms. CBT can also be directed at other problematic symptoms experienced by patients with CFS, such as chronic pain, depression, and poor sleep.

Graded Exercise Therapy

Graded exercise therapy (GET) has been demonstrated to be beneficial for patients with CFS [6, 7]. A Cochrane Study evaluating GET when compared to usual care or passive therapy found that GET probably has a positive effect on fatigue in patients with CFS [9]. GET is thought to work synergistically with CBT because it provides a practical context for the cognitive restructuring around fatigue that effective CBT encourages [10]. In one review of 12 studies of GET and CFS, it was determined that in order to obtain maximum benefit from GET, patients should be encouraged to focus on a time-contingent approach rather than symptom-contingent approach, as well as to engage in aerobic exercise as determined by an individually derived target heart rate [11]. Patients can also engage in a home exercise program of 5–15 min per session five times per week and gradually progress to up to 30 min [11]. Given the sensitivity of many patients with CFS to exertion, activity undertaken by patients with this diagnosis should be closely supervised by a medical professional, in order to prevent overexertion and worsening of fatigue.

Medication

Pharmacotherapy, including nutritional supplements, outside of the use of medication for specifically diagnosed comorbidities, has not been shown to be beneficial in CFS [6, 7, 12]. In one Australian study, patients with CFS reported taking a wide variety of prescribed medications such as sedatives and antidepressants in addition to over-the-counter supplements to gain relief from their symptoms [12]. A systematic review of pharmacologic therapies studied for the treatment of CFS found that no universal pharmacologic treatment can be recommended, citing the widely varied diagnostic and outcome criteria used between various studies [13]. Patients with CFS are often very sensitive to medication, and this in addition to the side effect profiles of many of these medications make them a less desirable treatment option for patients with CFS. On the other hand, it is crucial to treat comorbid conditions, particularly those that influence the patient's level of functioning. While the addition of an antidepressant or other medication in the absence of a diagnosis of a comorbid condition such as major depression has not been demonstrated to be helpful, when the diagnosis of depression is made, it is an important part of the patient's overall medical care [14].

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Referrals

Specialist involvement in the care of patients with fatigue should focus on the treatment of comorbid conditions and underlying causes as determined by history, laboratory workup, or physical exam. Additionally, rheumatology consult can be considered. It is important to remember, however, that the family physician plays a particularly important role in the care of patients with CFS, because coordinated care is central to the improvement in symptoms [7].

Patient Education and Activation

Patient education and involvement are central to the treatment of CFS. The patient's perception of fatigue and of their own self-efficacy plays a large role in determining their response to treatment of any kind; patient engagement and activation are absolutely critical to success [3].

Chronic Fatigue Syndrome in Children

Although CFS is thought to be less prevalent in children and adolescents than in adults, a wide range of prevalence of CFS in adolescents is thought to be between 0.11 and 1.29% found in Dutch, USA, and British populations [15]. As in adult populations, the diagnosis of CFS in children and adolescents is one of exclusion, and a detailed history and physical along with any indicated laboratory tests is indicated. In addition to the tests recommended for adults, serum ferritin should be strongly considered in children and adolescents presenting with fatigue. Two thirds of adolescents responded to CBT in one study after 6 months of treatment, and this treatment effect was sustained at 2–3-year follow-up [15]. Making a prompt diagnosis and getting children and adolescents into the appropriate treatment are of the utmost importance, as these determine the prognosis for the child's recovery [15].

Chronic Fatigue Syndrome in Elderly Adults

Fatigue is a prevalent concern in the elderly with some estimates of prevalence greater than 70% [16]. While fatigue does tend to occur with normal aging, it is important to rule out underlying conditions that may result in fatigue. It is estimated that up to two third of elderly patients presenting with fatigue will have a cause found on history, physical examination, and/or laboratory evaluation [16]. The same diagnostic criteria for CFS apply to the elderly as to the general adult population, but special attention should be paid to ruling out psychiatric and neurological conditions, including depression and dementia. In addition to this, special care should be taken in elderly patient populations to assure appropriate social support, especially if the diagnosis of CFS is made.

Chronic Fatigue Syndrome in Underrepresented Minority Populations

The prevalence of CFS is thought to be higher in minority groups, but the diagnosis in these patient populations can be more difficult if the family physician is not aware of the social and cultural context within which the patient presents [3]. One study in the UK looked at why the diagnosis is made less frequently in black and minority ethnic groups when compared to groups of white patients [17]. Their findings suggest that there was a lack of awareness of CFS among this patient population, lack of access to primary care, as well as incorrect assumptions and beliefs among physicians. They cited higher turnover of primary care physicians in inner city practices as well as lack of training in cultural sensitivity as contributing to this problem. They point to the importance of an ongoing relationship with a primary care physician as an important aspect of obtaining the correct diagnosis and providing quality care for this patient population [17].

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Family and Community Issues

CFS can produce both community economic hardship through the loss of occupational productivity but also family hardship in a family for whom one member is not able to fully participate in its day-to-day operation. Focusing on function and helping patients work with their families to improve their understanding of their illness and address their fatigue are ways in which family physicians can help patients to participate more fully both at home and at work.

Conclusion

Fatigue is a symptom that is commonly reported to the family physician, and CFS is an illness which helps family physicians conceptualize and treat fatigue for which no clear etiology can be found. Patients complaining of fatigue should have a thorough history, physical examination, and laboratory workup as outlined above. The diagnosis of CFS should be considered in any patient with fatigue for greater than 6 months and associated symptoms as outlined in the diagnostic criteria proposed by the Institute of Medicine. The workup of fatigue varies depending on the patient population and presenting complaints. It is important to evaluate fatigue in the context of the patients' social situation, emotional well-being, and ability to act with self-efficacy as these are all important things to be addressed if interventions are to be successful. Coordination of care and a strong therapeutic alliance predict success in the treatment of CFS.

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Care of the Patient with a Sleep Disorder

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J. F. Pagel

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General Principles

Definition/Background

We spend 1/3 of our lives in the reversible state of perceptual isolation called sleep. Unsurprisingly, disruptions and disorders of this primary physiologic state can lead to declines in quality of life, diminished waking performance, more frequent

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illness, as well as increases in disease morbidity and mortality. The spectrum of sleep disorders mirrors illnesses seen in the family medicine clinical population, so that most patients with sleep disturbance will receive their medical care in the primary care setting [1]. Despite high prevalence, sleep complains are often under-addressed by physicians. Recently, high-quality epidemiologic studies have documented the importance of the diagnosis and treatment of sleep disorders in primary care practice in order to reduce morbidity and mortality, improve comorbid disease processes, and improve patient quality of life [2, 3].

Classification

Sleep Disorders: The Clinical Spectrum

Sleep diagnoses range include those presenting primarily based on patient complaint (e.g., the insomnias) as well as those with strong negative affects morbidity and mortality yet effects on waking functioning that may be more difficult for the patient to understand and describe (e.g., sleep apnea). The primary sleep diagnoses are divided into six categories: insomnias, sleep-related breathing disorders, hypersomnias, circadian-rhythm sleep disturbance, parasomnias, and sleep-related movement disorders. Sleep disturbance is often secondary, associated with almost all chronic diseases that result in physical or mental discomfort for the patient, and incorporated into most psychiatric disorders as diagnostic criteria. Pregnancy and menopause, increasing age, and stress induce insomnia and sleep disruption. Pediatric sleep disorders are common.

The Insomnias

Background

Insomnia is a primary care problem. Thirty percent of the general population report symptoms of sleep disruption, and in the primary care clinic, more than 50% of patients have sleep complaints [4]. Diagnostically, over 40% of American adults occasionally struggle with insomnia, and 11–14% of the population have an ongoing problem with chronic insomnia [5]. Those at greatest risk include women and older adults. Insomnias is defined as the complaint of difficulty with sleep initiation, duration, consolidation, or quality; associated with daytime functional impairment. The daytime functional impairment in insomnia is most often fatigue, impaired memory or concentration, mood disturbance, daytime sleepiness, reduced motivation or energy, tension, headaches, or gastrointestinal symptoms. In adults, chronic insomnia can induce impaired social and vocational function and reduced quality of life. In severe cases insomnia may be associated with an increased risk of traffic and work site accidents as well as psychiatric disorders. In pediatrics, insomnia is most often an early childhood problem that develops when the child first attempts to sleep independently of parents [6].

Individuals with chronic insomnia consistently report lower values of quality of life on somatic/physical scales. Chronic insomniacs have an increased risk of depression and anxiety. Sleepless individuals are more likely to be obese. Chronic insomnia is also associated with increased pain in rheumatic disease with the degree of insomnia on any given night being a predictor of pain intensity the following day [7]. The annual direct cost of insomnia in the United States includes $1.97 billion for medications and 11.96 billion for healthcare services. Indirect costs include decreased productivity, higher accident rate, increased absenteeism, and increased comorbidity, with total annual cost estimates ranging from $30 to $107.5 billion [8].

Diagnosis

Diagnosing insomnia can be a complex task as the origin of a patient's insomnia is often multifactorial. Life stressors, concomitant illness, family, and social structure can precipitate symptomatic insomnia. The family medicine physician, who often has a more complete knowledge of these factors than the subspecialist, is in an ideal position to define the cause of the sleep–wake disturbance in a patient with insomnia. Insomnia is a subjective complaint with the diagnosis primarily based on a sleep history. Physical exam

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contributes little to the diagnosis and objective evaluation of sleep with polysomnography is rarely indicated. Evidence-based criteria for the evaluation and treatment of insomnia are summarized in Tables 1, 2, and 3 [9].

Treatment

Insomnia responds well to cognitive behavioral therapies (including sleep hygiene, sleep restriction, and behavioral approaches to treating conditioned insomnia). Sedatives including the barbituates and benzodiazepines induce sleepiness that extends into wakefulness after their use, induce tolerance, and have addiction potential. Sedating antidepressants and antipsychotics used for night-time sleep induction, also induce significant waking sedation. The newer GABA-specific site hypnotic medications have high efficacy, low toxicity, and minimal addictive potential. For patients with persistent insomnia, chronic use with the newer hypnotics can be justified and is indicated if medication use leads to improvement in waking performance. These hypnotic agents are less likely to have deleterious side effects than diphenhydramine the most commonly used OTC treatment for insomnia contraindicated for use in anyone over 65 years of age (Table 4) [11].

Table 1 Evidence-based symptom and diagnostic correlates for chronic insomnia

Chronic insomnia leads to poorer self-rated quality of life	A	Multiple large retrospective cohort studies
Chronic insomnia leads to increased health-care cost for affected patients	A	Multiple large retrospective cohort studies
Chronic insomnia predisposes an individual to mood disorder/depression	B	Large retrospective cohort study, longitudinal prospective study
Chronic insomnia is associated with decreased work productivity and increased time missed from work and/or school	B	Multiple small retrospective studies with consistent findings
Chronic insomnia leads to drug and alcohol abuse	C	Significant associated variables in adult and adolescent populations
Chronic insomnia leads to obesity	C	Small retrospective studies
Chronic insomnia is associated with an increase in automobile accidents	C	Retrospective review
Chronic insomnia is associated with an increase in mortality in geriatric patients	C	One large retrospective study
Chronic insomnia is associated with increased pain complaints in chronic pain patients	C	Retrospective review

Adapted and updated table from Pagel and Pegram [9]
Strength of recommendation based on Ebel et al. [10]

Table 2 Evidence-based recommendations for the diagnosis and treatment of insomnia

The evaluation of chronic insomnia does not require polysomnographic evaluation except when associated with other sleep-associated diseases such as OSA or PLMD	B	Consensus guidelines, usual practice, disease-oriented evidence, prospective diagnostic cohort study
Drug treatment of chronic insomnia with newer GABA-specific medications leads to improvements in associated sleep states and daytime performance	B	Retrospective cohort and case control studies with good follow-up
Drug treatment of chronic insomnia with newer GABA-specific medications can be maintained long term without loss of efficacy and without negative effects	B	Large prospective study (drug company)
Behavioral treatment of chronic insomnia leads to long-term improvements in associated sleep states and daytime performance	B	Retrospective cohort and case control studies with good follow-up consensus guidelines, usual practice

Adapted and updated table from Pagel and Pegram [9]
Strength of recommendation based on Ebel et al. [10]

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Table 3 Evidence-based criteria for sleep testing

Attended split night attended polysomnography indications		
(a) the diagnosis of sleep-related breathing disorders	A	Standard of care
(b) Positive airway pressure titration	A	Standard of care
(c) Pre- and postoperative evaluation of patients having surgery for obstructive sleep apnea	A	Standard of care
(d) Evaluation of patients being treated for OSA with persistent symptoms	A	High-quality cohort studies
(e) Patients with systolic or diastolic heart failure not responding to optimal medical management	A	Prospective diagnostic cohort studies
(f) Diagnosing restless leg syndrome/periodic limb movement disorder	C	Disease-oriented evidence
(g) Diagnosing insomnia in patients not responding to behavioral or medical therapy	C	Consensus guidelines
Treatment with PAP systems leads to reduced symptoms of sleepiness, increased quality of life, and lower blood pressure	A	Meta-analysis of retrospective cohort studies (standard of care)
Non-attended limited HST for the diagnosis of sleep-related breathing disorders	B	Retrospective cohort and case control studies with good follow-up (developing as standard of care)
Auto-titrating PAP for treating obstructive sleep apnea	B	Case control studies with good follow-up
Assessing daytime sleepiness (b) Diagnosing narcolepsy	B	Meta- analysis, usual practice, Disease-oriented evidence

Adapted table from Pagel and Pegram [9]

Table 4 Hypnotics agents utilized to induce sleep with minimal next day sleepiness after US: Evidence based on pharmacodynamics, clinical trials, and/or performance testing

Drug & class	1/2 life	Next day sleepiness [clinical trials]	Toxicity and/or significant side effects
Short acting gaba agonist Triazolem	1–2 h	Anecdotal and per survey [placebo equivalent]	Antegrade amnesia, confusion at higher dose
Gaba selective agents Zaleplon	1 h	[placebo equivalent]	No consistent reports [not in widespread use]
Zolpidem	1.5 h	Anecdotal [placebo equivalent] Per survey when dosed outside pharmacodynamic profile and in the elderly	Symptomatic Parasomnias, Next night rebound insomnia
Eszopiclone	6 h	Anecdotal [placebo equivalent]	Possible parasomnia associations

The Sleep-Associated Breathing Disorders

Background

Obstructive sleep apnea (OSA) is a physiologically disruptive and dangerous sleep diagnosis. OSA has a strong association with pulmonary, cardiac, endocrine, cognitive, and psychiatric disease [12]. In patients with OSA, continued breathing effort occurs despite obstruction of the airway associated with inadequate ventilation. OSA is more common among men, snorers, the elderly, and among those who are overweight. Worldwide, more than 700 million individuals now have a BMI $>$ 30 [9]. This level of obesity and an increasingly aging population have led to an epidemic of this physiologically dangerous diagnosis. The symptoms of OSA include persistent snoring (80%), daytime sleepiness (22–32%), and apneas observed by bed partners or caregivers (in adults, the report of observed apnea often

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indicates the present of severe apnea). OSA is present at high frequency (24–34%) in the adult primary care clinic population and must be suspected in any patients with comorbid diagnoses known to be associated with apnea [12] (Table 5).

Adult OSA has a clear association of daytime cognitive impairment (i.e., daytime sleepiness) contributing to a significantly higher rate of motor vehicular accidents in untreated patients [13]. Recent epidemiological studies have cross-matched sleep apnea evaluation with long-term prospective cardiovascular risk, pointing out the consistent and strong association between OSA and essential hypertension, increased mortality, congestive heart failure (both right and left sided), myocardial infarction, and cerebral vascular accidents [12]. Recent studies have emphasized the clinical significance of the association between atrial fibrillation and untreated OSA [14]. OSA can contribute to insulin resistance and metabolic syndrome [15]. Treatment of OSA can produce an improvement in PTSD symptoms among individuals who have both diagnoses [16] (Table 6).

Diagnosis and Treatment

In most cases in order to diagnose and treat OSA polysomnography (PSG), the recording of multiple physiological signals during sleep including channels of electroencephalography (EEG), electrooculogram (EOG), and chin electromyogram (EMG) is required. A PSG includes sleep staging as well as recordings of respiratory effort, airflow, pulse oximetry, snoring, sleep position, ECG, leg EMG, and video monitoring. Additional channels are sometimes utilized including end-tidal or transcutaneous CO_2 and additional EEG channels if potential nocturnal seizure disorders are being evaluated. The clinical indications for PGG are summarized in Table 3.

OSA is most often treated with devices that hold the airway open during sleep by utilizing positive airway pressure (PAP). This treatment is well tolerated by most OSA patients with few side effects and documented reductions in morbidity, hospitalization, and health-care utilization [17]. In evaluating OSA, a split night protocol is often utilized in which a therapeutic treatment or titration portion of the PSG is added during the night of study after a period of diagnostic sleep time. A PSG report includes data as to sleep architecture, respiratory parameters (number and index of apneas [episodes of complete respiratory cessation], hypopneas [episodes of reduced respiratory drive and hypoxia], and respiratory-related arousals), periodic limb movements, a description of any parasomnia or seizure activity, EKG abnormalities, and the results and appropriate setting for any treatment attempted during the night of study.

Alternative approaches to PSG include home screening tests (HSTs), an approach that has been shown to be particularly useful in younger patients without comorbid diagnoses [18]. These

Table 5 Clinical diagnoses associated with OSA including the approximate % of adult patients in each category with apnea–hypopnea index (AHI) > 5.0 events per hour

Obesity – 40–75%
Morbid obesity >80%
Excessive daytime sleepiness – 60–80%
Hypertension – 40–80%
Myocardial infarction (CAD) – 60–70%
Cerebral vascular accident – 60–70%
Atrial fibrillation – 60–80%
Chronic pain treated with opiates – 70–80%
Congestive failure (right and left sided) – 70–80%
Metabolic syndrome – 80%
Diabetes – 40–60%
Posttraumatic stress disorder – 60–80%

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Table 6 Evidence-based associations of obstructive sleep apnea (OSA)

Adult OSA	Obesity	A – consistent systemic meta-analyses
	Cognitive impairment (daytime sleepiness)	A – Consistent systemic meta-analyses
	Motor vehicular accidents	A – Consistent systemic meta-analyses
	Hypertension	A – Cross-sectional analysis of prospective cohort studies, consistent systemic meta-analyses
	Increased mortality	B – Retrospective cohort studies
	Congestive heart failure (right and left sided)	B – Cross-sectional analysis of prospective cohort studies, inconsistent systemic meta-analyses
	Coronary artery disease	B – Cross-sectional analysis of prospective cohort studies, retrospective diagnostic cohort study
	Cerebral vascular accidents	B – Cross-sectional analysis of prospective cohort studies, retrospective cohort study
	Metabolic syndrome	B – Cross-sectional analysis of prospective cohort studies, retrospective cohort studies
	Atrial fibrillation	B – Multiple retrospective cohort studies and treatment follow-up studies
	PTSD	B – Multiple retrospective cohort studies with positive response to PAP therapy
	Diabetes	C – Retrospective cohort studies
	Other cardiac arrhythmias	C – Case series, usual practice
Pediatric OSA	Poor school performance	B – Multiple retrospective cohort studies
	Downs syndrome	B – High frequency of OSA (50–100%) in multiple small retrospective studies, positive response to therapy
	Enuresis	C – Retrospective cohort studies
	Failure to thrive	C – Case series, usual practice
	Learning disability	C – Retrospective cohort studies
	Obesity	C – Retrospective cohort studies
	Attention deficit/ hyperactivity disorder	C – Inconsistent retrospective cohort studies

Adapted table from Pagel and Pegram [9]
Strength of recommendation based on Ebel et al. [10]

studies have limitations. They cannot determine whether the patient is actually asleep during the recording, and in patients with insomnia the number of respiratory events (apneas and hypopneas) per hour will be lower than actually present due to recording time that will be in wake. Periodic limb movements and arousals from events such as parasomnias are not recorded by HSTs, and most home screeners differentiate poorly between obstructive and central apneas. Central sleep apneas (CSA) are nonobstructive apneas in which the individual exerts no respiratory effort. CSA is less common than OSA presenting most often in patients with CHF; post-ICU patients; those with a history of significant cardiovascular, pulmonary, or CNS disease; development abnormalities; opiate use; the extreme elderly; and those living at elevations above 6500 ft. [19, 20]. Treatment includes the addition of oxygen or backup rate systems to PAP therapy. HST can be coupled with PAP auto-titration to avoid full PSG testing. Auto-titrating pap systems are tolerated well by some patients; however, these systems have minimal diagnostic capacity and can report inappropriate settings for misdiagnosed patients and patients with central apnea and/or nasal congestion or mouth leaks on pap therapy [21]. OSA can also be treated with dental mouthpieces and ENT surgery, approaches that reduce rather than eliminate (as with PAP) the number of apnic events [22].

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In pediatric patients, OSA is most clearly associated with tonsillar hypertrophy. OSA can contribute to poor school performance [23]. Studies also support the association of pediatric OSA with failure to thrive, obesity, enuresis, attention deficit/hyperactivity disorder, Downs Syndrome and other developmental disorders, and learning disability. The treatment of pediatric OSA is most often surgical – (T&A).

Excessive Daytime Sleepiness (Other Hypersomnias)

The National Health and Safety Administration (NHTSA) in 1999 estimated that 9.5% of police-reported crashes and 4% of all traffic crash fatalities involved drowsiness and fatigue as contributing causes. Beyond the personal and social loss associated with these accidents, the cost of untreated daytime sleepiness was estimated at $12.5 billion based on workplace loss and loss of productivity [23]. The most common causes of daytime sleepiness are sleep deprivation and the use of prescription and nonprescription agents as well as drugs of abuse that induce daytime sleepiness (daytime sleepiness is among the most common of medication side effects) [24]. The next most common cause is untreated OSA. The other sleep disorders such as narcolepsy that induce daytime sleepiness occur at a much lower frequency (2/1000). The hypersomnias generally require both PSG and multiple sleep latency testing (MSLT) for diagnostic evaluation and assessment of daytime sleepiness. The MSLT includes four to five opportunities to nap in the sleep laboratory after a full-night PSG with EEG, EOG, and EMG monitored, so that sleep and REMS onset can be determined. MSLT reports should include average or mean latency to sleep and the number of sleep onset REMS periods recorded (diagnostic criteria for narcolepsy). Medications used in somnolent patients to induce alertness include the amphetamines (medications with high abuse potential) and newer alerting agents (e.g., modafinil) that have a lower potential for abuse and negative side effects.

Circadian-Rhythm Sleep Disorders

The biological clock for sleeping is based in part on the circadian rhythm of sleep and wake propensity. Chronic sleep disturbance can result from disruptions in this system or from misalignments between an individual's circadian rhythm and the 24-h social or physical environment. Delayed sleep-phase syndrome (DSPS) in which individuals go to bed and rise later than the general population is symptomatic in 7–16% of adolescents. Shift work disrupts normal sleep patterns for approximately 20% of the population. At least 10% of individuals evaluated in sleep laboratories for chronic insomnia have a definite circadian component to their disorder [8]. Melatonin is the photoneuroendocrine transducer that conveys information controlling sleep–wake cycles and circadian rhythms in the central nervous system (CNS). Low doses coupled with bright-light therapy are useful in treating these disorders [26]. Jet lag and shift work disorders can also be effectively treated with repetitive short-term use of sedative/hypnotics [27].

Parasomnias

Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep. Parasomnias encompass sleep-related movements, behaviors, perceptions, emotions, and disturbed dreaming – sleep-related behaviors and experiences in which the sleeper has no conscious deliberate control. Parasomnias become clinical diagnoses when associated with sleep disruption, nocturnal injuries, waking psychosocial effects, and adverse health effects. Many parasomnias are sleep state specific. Recurrent nightmares (the most common of the parasomnias) occur in 15–40% of normal adolescents. A wide spectrum of medications is known to induce nightmares (diphenhydramine, nicotine, and SSRI antidepressants are common culprits) [28]. Recurrent, disturbing nightmares are the most common symptom of posttraumatic stress disorder (PTSD).

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REM behavior disorder (RBD) in which the motor block that usually prevents the acting out of dreams is lost, is most common in late-middle-age males and in patients with progressive neurological disease (e.g., Parkinson's disease). RBD occurs in 0.38–0.5% of the population [1]. The arousal disorders of somnambulism (sleep walking, night terrors, and confusional arousals) are reported by 4% of pediatric patients. Since pediatric parasomnias often disappear with the onset of puberty, treatment is most often bed-site protection and parental reassurance. Enuresis is present in 15–20% of 5-year-old children declining to 1–2% in young adulthood.

Sleep-Related Movement Disorders

More than 12 million people in this country experience unpleasant, tingling, creeping feelings in their legs during sleep or inactivity as a symptom of a disorder called restless legs syndrome (RLS). This disorder causes an uncontrollable urge to move and to relieve the sensations in the legs. Sleep in these patients is often disrupted by periodic limb movements occurring in the extremities during sleep that can be detected by PSG. Low dosages of dopamine precursors and dopamine receptor agonists at bedtime have been demonstrated to be efficacious in these disorders [29].

The Family Physician and Sleep Medicine

On any given day up to 90% of adult patients visiting their primary care physician are experiencing sleep-related symptoms. At least 1/3 are likely to have OSA. Currently, despite the known increases in morbidity and mortality associated with this diagnosis, only 4% of the individuals likely to have OSA have been tested. Approximately 14% of the general population suffer from chronic insomnia, with 1/3 of the population reporting occasional symptoms. Up to 15% of adults suffer from RLS/PLMD [29]. Payers, concerned with the potential cost of evaluating and treating this large number of patients, have pushed sleep medicine diagnosis and treatment into the primary care setting where family physicians and physician extenders are expected to make correct diagnoses and monitor appropriate treatment. Sleep medicine consultation for difficult patients is available in many communities, and the same standard of care is expected even when diagnosis is limited to screening questionnaires, an approach known to have low sensitivity and efficacy, and treatment approaches with known limitations [30].

Few primary care physicians routinely address sleep complaints or screen for OSA. Questionnaires can be an excellent tool for obtaining information about sleep disorders, but even when sleep complaint questionnaires are highlighted on patient charts, patients at high risk for are infrequently evaluated. Studies from outside the USA indicate the potential for primary care sleep medicine. Primary care physicians with limited training in sleep medicine were shown to provide a level of care for patients with suspected OSA in South Australia comparable to that provided in the University Sleep Medicine Center in Adelaide [30]. There are a huge number of patients with sleep-associated diagnoses affecting their mortality and morbidity. The current care system has been able to address OSA in only a small percentage of the affected individuals. Sleep-associated diagnoses negatively affect the medical and psychiatric disorders most often seen in family medicine: hypertension, obesity, cardiovascular disease, arrhythmias, mood disorder/depression, and anxiety. The associated personal and medical costs of untreated sleep disorders are staggering. Associated daytime sleepiness negatively affects driving and work performance and when untreated contributes to a large number of motor vehicular accidents, injuries, and deaths. Sleep medicine care is migrating into the primary care arena where the HST is beginning to be a clinical test as commonly utilized as EKG's and pulmonary function tests.

A majority of individuals that suffer from disorders of sleep and wakefulness are undiagnosed and untreated. Primary care physicians have access to this large grouping of at-risk patients as well as training and experience in the full extent of

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medical and psychiatric illness affecting patients with sleep disorders. Family physicians often have close relationships with their patients and an awareness and understanding of the biopsychosocial context, an awareness often unapparent to the sub-specialist sleep physician. Family Medicine Physicians with an interest in sleep medicine can qualify for a CAQ qualifying them to interpret polysomnography reports and function as specialists in the field.

Prevention

Sleep disorders are extremely common and rarely addressed in many primary care practices, yet to date, the United States Preventive Services Task Forces, the American Academy of Family Physicians, and the Center for Disease Control have not recommended routine screening. This recommendation, made despite high incidence and excellent epidemiologic data as to negative and costly effects of sleep disorders, especially OSA, on morbidity and mortality, was made based on two factors: (1) the low sensitivity and specificity of inexpensive questionnaires designed to screen for OSA, and (2) the cost of HST screeners and polysomnography used to diagnose OSA. Current recommendations are that OSA should be considered as a potential diagnosis in every patient who has a diagnosis with high-frequency OSA comorbidity (obesity, hypertension, daytime sleepiness, cardiac disease, arrhythmias, chronic pain treated with opiates, CVA, CHF, and PTSD) (Table 3) [31].

A spectrum of poor sleep hygiene practices can induce insomnia, especially in high-risk populations such as adolescents and the elderly. High stress behavior, nicotine, caffeine, and the nocturnal use of electronic systems contribute to complaints of insomnia.

Family and Community Issues

Sleep disorders, including the common diagnoses of OSA and insomnia, are commonly found in family members based on both genetic and social factors. Daytime sleepiness in pediatric age groupings is associated with poor school performance. In adolescents, early school start times induce sleepiness and negatively affect school performance in a population prone to DSPS and social sleep deprivation [32]. In adults, daytime sleepiness whether based on OSA, sedating medication use, sleep disruption, or neurological disease is associated with a significantly higher level of motor vehicular and work-related accidents. This is a particular problem for shift workers and those who must drive for a living.

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Medical Care of the Surgical Patient

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Introduction

Millions of Americans undergo surgery every year [1]. These patients must then turn to their primary care provider to undergo a preoperative evaluation. This preoperative evaluation allows the provider and the patient to optimize underlying conditions to improve surgical outcomes and minimize complications. The preoperative evaluation is not meant to clear the patient for surgery, but rather to evaluate and when necessary implement measures to better prepare high-risk patients for surgery [2]. An evaluation focusing on cardiac, pulmonary, infectious, and hematologic risk factors and determining the patient's functional capacity are essential elements for stratifying surgical risk [2].

Preoperative History

Any preoperative evaluation begins with details of the planned surgery. This entails the planned procedure, indication, surgery date, surgeon's name, and practice location. Obtaining a thorough history is an integral part of the preoperative evaluation. When discussing the patient history it is important to review all past and current medical problems, medications, previous surgeries as well as any previous surgical complications including personal or family history of reactions to anesthesia especially malignant hyperthermia or delayed awaking [3]. In children the history should include birth history, gestational age at birth, perinatal complications, congenital chromosomal or anatomic malformations, and history of recent infections [2]. If a patient has moderate or severe cardiac valvular disease, implanted cardiac devices, congenital heart disease, or severe pulmonary hypertension, current guidelines recommend evaluation by a specialist prior to a planned surgery [1, 4]. If the above conditions are not present, a preoperative evaluation completed by a primary care provider is appropriate. The majority of surgical morbidity and mortality complications generally fall into cardiac, pulmonary, infectious, or hematologic categories [2].

Cardiac Assessment

Surgical Risk

Once you have determined a patient is appropriate for preoperative evaluation to be completed by a primary care physician, you can move on to clinical assessment. Surgical risk is related to the degree of hemodynamic instability expected during the surgery or procedure [5]. Surgical risk is stratified by the American College of Surgeons into three categories and is based on the estimated 30-day cardiac event rates [5, 6] (See Table 1). Low-risk surgeries include ambulatory surgeries, breast, endoscopy, and cataract surgery. These are classified as low risk as their risk of cardiac death or nonfatal myocardial infarction (MI) is $<1\%$. Intermediate risk surgeries include surgeries that involve peripheral vascular structures, intrathoracic, intra-abdominal, head and neck surgeries, and orthopedic surgeries. Intermediate risk surgeries carry a 1–5% risk of cardiac death or nonfatal MI. Finally high-risk surgeries include any aortic or major vascular surgeries. These carry $>5\%$ risk of cardiac death and nonfatal MI [5, 6].

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Table 1 Noncardiac procedure risk [1, 6]

Surgical Risk of Cardiac Death and Nonfatal MI in Noncardiac Procedures	
Risk of Procedure	Examples
High >5%	Aortic and major vascular surgery
Intermediate 1–5%	Intraperitoneal or intrathoracic, carotid endarterectomy, head and neck surgery, orthopedic surgery
Low risk <1%	Cataract, breast, endoscopy, ambulatory surgery

Risk Stratification

Risk stratification is dependent upon the patient's underlying health and the nature of the planned surgery. The American College of Cardiology/American Heart Association (ACC/AHA) recommends using a validated risk-prediction tool to predict risk of perioperative complications [1]. One of the highly utilized risk calculators is the Revised Cardiac Index (RCI). This calculator stratifies a patient's risk based on five clinical variables plus the surgical procedure being performed [1]. Each variable present increases the cardiac complication rate, which is defined as death, nonfatal MI, or cardiac arrest [1]. The presence of three or more factors carries a greater than 15% risk for cardiac complications. The RCI calculator is favored among clinicians as it is easy to implement and easy to interpret which makes it a valuable tool for preoperative assessment [1] (Table 2).

A second and newer calculator was developed by the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP). This calculator was developed based on data encompassing more than one million operations and multiple surgical centers [1, 7]. The calculator uses the CPT code of the procedure being performed as well as 21 patient-specific variables. Variables include age, sex, BMI, dyspnea, steroid use, previous MI, and severe COPD, among others. Using the above variables the calculator provides an estimation of patient specific complication risk for cardiac, infectious, pulmonary, and even death compared to population averages [7]. An estimate of hospital stay and likelihood for need to discharge to a nursing or rehabilitation facility is also provided.

Functional Capacity

An important part of the preoperative history is to determine functional capacity. Functional capacity is important to discuss as it is a good predictor of perioperative cardiac complications [1]. A patient's functional capacity can be estimated by their activities of daily living. Functional capacity is often expressed as metabolic equivalents (METs). Functional capacity is described as excellent (>10 METs), good (7–10 METS), moderate (4–6 METs), or poor (<4 METs) [1]. Inability to perform activities of at least 4 METs in daily activities is correlated with increased perioperative complications [1]. Examples of activities <4 METs include: golfing with a cart, playing a musical instrument, and slow ballroom dancing [1, 8]. In contrast patients with a functional capacity greater than 4 METS are unlikely to have postoperative cardiovascular complications even if cardiac risk factors exist. Examples of activities with >4 METs include: climbing a flight of stairs, walking up a hill, and performing heavy housework (Table 3) [1, 8].

The Duke Activity Status Index (DASI) is a good self-administered questionnaire that can be used to assist the clinician in determining a patient's functional capacity [8] https://www.mdcalc.com/duke-activity-status-index-dasi.

Pulmonary Assessment

The incidence of pulmonary complications following surgery varies widely and is estimated to be between 1% and 23% [9, 10]. Preoperative risk factors for postoperative pulmonary complications (PPC) include age, type of surgery,

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Table 2 Revised Cardiac Risk Index [1]

Revised Cardiac Risk Index	
High risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular surgeries)	1 point
History of ischemic heart disease	1 point
History of congestive heart failure	1 point
History of cerebrovascular disease	1 point
Preoperative treatment with insulin	1 point
Preoperative serum creatinine >2.0 mg/dL	1 point
RCRI Score	**Risk of major cardiac event**[a]
0 points	3.9% (2.8–5.4%)
1 point	6.0% (4.9–7.4%)
2 points	10.1% (8.1–12.6%
≥3 points	15% (11.1–20.0%)

[a]Major cardiac event defined as death, nonfatal MI, or cardiac arrest within 30 days of noncardiac procedures

Table 3 Functional assessment [1, 5]

Functional Assessment METs		
	Metabolic Equivalents	Examples
Poor	<4	Vacuuming, activities of daily living, 2 mph walking
Moderate	4–6	Climbing flight of stairs, cycling, 4 mph walking
Good	7–10	Hiking, leisure swimming, ballroom dancing
Excellent	>10	Jogging, singles tennis, scrubbing floors

functional status, smoking, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, and maybe nutritional status [10]. Age greater than 65 and poor functional status both increases the risk for postoperative pulmonary complications and infections.

Patients enrolling in smoking cessation programs at least 8 weeks prior to surgery decreased their risk for PPC. This time frame allowed for recovery of the mucocilliary transport mechanism within the lung to recover, thus decreasing secretions [9, 10]. Cessation of smoking less than 8 weeks is of questionable benefit and may have an increased complication rate.

Asthma and COPD should be under control prior to surgery with routine prescribed use of bronchodilator and/or steroid inhalers. Guidelines do not define a degree of pulmonary impairment that would prohibit surgery [2, 10]. Routine ordering of pulmonary function tests is therefore not warranted.

Obstructive sleep apnea (OSA) increases the risk for airway management difficulties in the postoperative period and all patients undergoing surgery should be screened for undiagnosed OSA [10, 11]. It has been estimated that approximately 60% of surgical patients with moderate to severe obstructive sleep apnea were undiagnosed [12]. Obstructive sleep apnea has a very high prevalence in the United States, the majority of which is undiagnosed. Though its influence on postoperative pulmonary complications has not been well studied, OSA is associated with several comorbidities including hypertension, diabetes, obesity, cerebrovascular and myocardial disease, placing the patient at higher risk for postoperative complications including unplanned re-intubations [11, 12]. To screen for OSA a relatively quick and efficient screening tool has been developed called the STOP-BANG questionnaire (Table 4) [12]. It consists of four subjective yes or no questions and four objective findings to arrive at a score of 0–8. The first four questions are related to sleep disturbances (snoring, tiredness, witnessed apnea periods, and high blood pressure). The remaining four questions are patient specific and include BMI ≥35 kg/m^3, age ≥50, neck circumference ≥40 cm or 15.75 in, and male gender. Each "yes" answer is one point. A score ≥5 is high risk for OSA, score of 3–4 is intermediate risk and score ≤2 is low risk [12]. A patient with a low score is very unlikely to have

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Table 4 Obstructive Sleep Apnea Screening Tool [4, 12]

STOP-BANG Questionnaire	
1. **Snoring**. Have you been told that you snore during sleep?	1 point
2. **Tiredness**. Do you feel overly tired or fatigued during the day?	1 point
3. **Observed Apnea**. Have you been told you stop breathing while you sleep?	1 point
4. **Blood pressure**. Do you have elevated blood pressure?	1 point
5. **BMI ≥35 kg/m^3**	1 point
6. **Age ≥50 years**	1 point
7. **Neck circumference ≥40 cm**	1 point
8. **Male Gender**	1 point
Low risk	0–2 points
Intermediate risk	3–4 points
High risk	≥5 points

OSA and similarly a patient with a high score is very likely to have OSA. Patients who fall in the intermediate range are more likely to require further testing to confirm the diagnosis of OSA, which can be done using polysomnography or an overnight sleep study [12].

Several studies have indicated an increased risk for PPC in patients with low serum albumin levels [10, 11]. Those patients with poor functional status, limited financial resources, absent social support structure and the elderly are at highest risk for malnutrition. If there are nutritional concerns, preoperative nutritional supplementation can be provided prior to surgery. Though the exact duration of supplementation needed is uncertain, it has been suggested that a minimum of 7–15 days is required to provide benefit [2].

Upper abdominal and intrathoracic procedures are known to produce marked alterations in pulmonary function. The adverse effects on chest wall mechanics predispose patients to atelectasis and retained secretions [10]. Deep breathing exercises and incentive spirometry in the postoperative period may be beneficial in decreasing PPC in obese patients, those with lung disease, or those undergoing abdominal or thoracic procedures [2, 10].

Infection Assessment

Numerous risk factors have been identified for the development of surgical site infections (SSI) after surgery. Potentially modifiable patient risk factors include glycemic control, nutrition status, obesity, smoking status, alcohol use, immunosuppression, and total bilirubin >1.0 mg/dL [13]. Optimal blood glucose control should be encouraged for all patients; however, there is some evidence that short-term glucose control can be more impactful than long-term control of hemoglobin A1C. Target perioperative blood glucose should be between 110 and 150 mg/dL except in cardiac surgery patients where the target blood glucose is <180 mg/dL [13]. Blood glucose levels <110 mg/dL have not shown to decrease SSI rates and may be tied to an increase in adverse events [13]. All patients should be counseled to stop smoking. In this time period smoking cessation improves wound healing and decreases infection risk and other postoperative complications. In addition to PPC, malnourished patients are also at increased risk for SSI and as such patients should be screened for risk factors as previously outlined [13].

Though the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) within the community has increased dramatically in recent years, universal screening guidelines for MRSA have not been developed. However, the American Society of Health System Pharmacists recommends screening and nasal mupirocin decolonization for *S. aureus* for all patients before total joint replacement and cardiac procedures [13]. Typical preoperative decolonization includes the use of 2% nasal mupirocin twice daily for 5 days [13].

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Endocarditis Prophylaxis

Infective endocarditis is a rare but life-threatening disease [14]. Due to the high levels of morbidity and mortality associated with infective endocarditis preoperative antibiotic prophylaxis has been common place for many years. Infective endocarditis is thought to develop after a transient bacteremia as a result of mucosal irritation especially the oral mucosa, GI tract, urethra, and vagina. Common pathogens include strep viridians, streptococcal species, and staphylococcal species [14, 15].

The American Heart Association/American College of Cardiology (AHA/ACC) state that antibiotic prophylaxis for high-risk patients undergoing procedures likely to result in bacteremia with a microorganism that has the potential ability to cause endocarditis is reasonable [15]. Routine prophylaxis for gastrointestinal (GI) or genitourinary (GU) procedures, even for patients with high-risk cardiac conditions, is not generally recommended [15]. High-risk patients include: patients with a history of infective endocarditis and patients with a prosthetic valve, congenital heart disease, and heart transplant patients [15]. Moderate-risk patients include: history of rheumatic fever, patients with native valve disease (bicuspid aortic valve, mitral valve prolapse, and calcified aortic stenosis), and patients with unrepaired congenital anomalies [15]. Current recommendations are based on case reports and small studies. For patients who are considered at risk for infective endocarditis antibiotic prophylaxis is recommended if undergoing the following procedures: dental procedures with gingival manipulation, respiratory procedures, and dermatologic or musculoskeletal procedures involving infected skin or tissue [15]. Appropriate antibiotic prophylaxis regimens that are preferred include: amoxicillin 2 grams orally as a single dose, 30–60 min prior to procedure in the non-penicillin allergic patient or clindamycin 600 mg orally also as a single dose 30–60 min prior to the procedure in penicillin allergic patients [15]. See Table 5.

Hematologic Assessment

When screening for perioperative hematologic disorders that may impact surgical management, assessment should ascertain risks related to the presence of anemia, polycythemia, bleeding, and/or clotting disorders. History should inquire to the presence of kidney disease, liver disease, inflammatory/autoimmune disorders, menstrual disorders or excessive bleeding, risk for nutritional deficiencies, signs/symptoms of anemia, and tobacco and alcohol use [6]. When discussing the patient history it is important to include a personal or family history of excessive bleeding or frequent blood clots. Need for further testing such as complete blood count or coagulation studies should be driven by the underlying history.

Venous thromboembolism (VTE), including pulmonary embolus (PE), is a major cause of morbidity and mortality in postoperative patients [16]. About 50% of all venous thromboembolism events occur as a result of a current or recent hospital admission for surgery or acute medical illness [17]. When performing a preoperative

Table 5 Antibiotic regiments for preoperative prevention of endocarditis [15]

Patient Scenario	Medication	Dose[a]
Able to take orals and no PCN allergy	Amoxicillin	2 g oral
PCN allergic	Cephalexin	2 g oral
	Clindamycin	600 mg oral
	Azithromycin or Clarithromycin	500 mg oral
Unable to take oral medications	Ampicillin	2 g IM or IV
	Cefazolin or Ceftriaxone	1 g IM or IV
Unable to take oral medications and PCN allergic	Cefazolin or Ceftriaxone	1 g IM or IV
	Clindamycin	600 mg IM or IV

[a]Single dose regimen 30–60 min prior to procedure

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evaluation it is important to review with the patient their risks for deep vein thrombosis. Patient risk factors include: obesity, previous VTE, cancer, age >60, prolonged immobilization, use of hormonal therapy, and comorbid conditions such as stroke, congestive heart failure, or myocardial infarction [16]. Some patients may have inheritable hypercoagulable states and that must be documented to inform the surgical team. Inherited abnormalities include deficiencies in protein c, protein s, or antithrombin, Factor V Leiden mutation, and prothrombin mutation [16]. The postoperative period is the perfect setup for VTE complications due to prolonged immobilization, endothelium disruption, and the patient's preexisting chronic or underlying diseases [16]. The perioperative evaluation is an ideal time for discussing the plan for postoperative VTE prophylaxis.

Prevention of Deep Vein Thrombosis

To prevent venous thromboembolism in the postoperative period thromboprophylaxis with both mechanical and pharmacologic means can be utilized [18]. Mechanical methods utilize compression stockings and pneumatic compression devices on the lower limbs to prevent venous stasis and promote venous outflow. Pharmacologic options include unfractionated heparin (UFH), low molecular weight heparin (LMWH), warfarin, antiplatelet agents, and novel oral anticoagulants (NOACs) [17, 18]. Pharmacologic thromboprophylaxis is utilized for moderate-risk and high-risk patients undergoing moderate- or high-risk surgeries [18].

There are two medications that are preferred for thromboembolism prophylaxis: low molecular weight heparin (LMWH) and low dose unfractionated heparin (LDUH) [17, 18]. Heparin is administered subcutaneously as 5000 Units every 8 or 12 h. Mechanism of action of heparin is via inhibition of antithrombin III (antithrombin) [16]. The mechanism of action of LMWH is via inactivation of factor Xa, but they have little effect on thrombin [16]. Types of LMWH that are approved for use in the United States include: enoxaparin, dalteparin, and tinzaparin [16]. Multiple studies have shown that both LMWH and LDUH are equally effective in prevention of VTE and PE [18]. Choice of agent is usually dependent on hospital preference and cost.

Risk of venous thromboembolism varies depending on patient characteristics and the type of surgery. High-risk surgeries include: major orthopedic surgery of lower limbs, particularly hip or knee, surgery for cancer, neurosurgery, acute spinal cord injury, and multiple trauma [16]. Recommendations for prophylaxis can be broken down into the type of surgery: general (including gynecologic and urologic), orthopedic, and neurosurgery.

General Surgery

General surgery category encompasses patients who undergo gastrointestinal, urological, gynecologic, bariatric, vascular, plastic, or reconstructive surgery. The 2012 American College of Chest Physicians (ACCP) guidelines use both the Rogers and Caprini score to determine a patients individualized risk for VTE [18]. In patients who are scheduled for general surgery and are a very low risk for VTE (Rogers score <7 or Caprini score, 0), no specific pharmacologic or mechanic prophylaxis is recommended, instead early ambulation and mobilization is encouraged [18].

For patients who are at low risk of VTE (Rogers score 7–10; Caprini score 1–2) ACCP guidelines recommend mechanical prophylaxis [18]. For patients who fall into a moderate-risk or higher category who are not at elevated risk for bleeding, it is recommended to receive pharmacologic prophylaxis in the form of LMWH in addition to mechanical prophylaxis (Rogers score >10, Caprini score >3) [17, 18].

The clinical situation becomes more complicated for those patients who are at high risk for VTE and who are also at high risk for bleeding. For patients in this category the recommendation would be to use mechanical prophylaxis only until pharmacologic prophylaxis can be safely used [18]. Ultimately this is a decision to be made by the surgical team, anesthesia team, and the patient.

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Orthopedic: Hip and Knee Arthroscopy and Hip Fracture Surgery

In patients who undergo elective hip or knee arthroscopy or hip fracture surgery, guidelines suggest a minimum of 10–14 days of thromboprophylaxis and up to potentially 35 days [18]. The preferred anticoagulant is LMWH due to the safety and effectiveness profile [18]. However, guidelines do not specify a preference of LMWH, LDUH, aspirin, VKA, or intermittent pneumatic compression device [18]. If pharmacologic prophylaxis is utilized, then it is recommended that these medications be started no sooner than 12 h postoperatively [18]. Similarly the ACCP recommends dual thromboprophylaxis with a pharmacologic and mechanical device during the acute hospitalization [18].

Craniotomy and Spinal Surgery

For craniotomy patients and those undergoing spinal surgery, the recommendation would be to use mechanical prophylaxis with intermittent pneumatic compression device over pharmacological prophylaxis, unless the patient is very high risk for VTE [18]. For high-risk patients the recommendation would be to initiate mechanical prophylaxis adding pharmacological prophylaxis once adequate hemostasis is established and the risk of bleeding decreased [18].

Preoperative Testing

Preoperative testing is often ordered by primary care physicians prior to any planned surgical intervention. The decision to order preoperative testing is based on patient history, examination findings, and oftentimes surgeon preference. These tests allow for providers to properly assess surgical risk and prepare for possibility of postoperative complications [2, 6].

Electrocardiogram (EKG)

Preoperative EKG testing should be ordered in any patient scheduled for surgical intervention with history of coronary artery disease, active symptoms of cardiovascular disease, or undergoing a high-risk surgery, where the perioperative cardiac risk is greater than 5% [1, 2, 6]. Also widely accepted is the recommendation to abstain from EKG testing in any patient undergoing low-risk surgery with a less than 1% perioperative cardiac risk [1]. See Table 1 for noncardiac surgery procedure risk. To help decide then if patients undergoing an intermediate risk procedure without active cardiovascular symptoms should undergo EKG testing, the use of a surgical risk stratification tool such as the Revised Cardiac Risk Index (RCRI) can be helpful [1] (Table 2). If a patient has one of the clinical risk factors within the RCRI (cerebral vascular disease, congestive heart failure, creatinine level >2.0 mg/dL, diabetes mellitus requiring insulin, and ischemic cardiac disease), it is recommended to obtain a preoperative EKG [1]. Patients with two or more clinical risk factors are at significant higher risk for a major cardiac event [1].

Echocardiogram

For patients with dyspnea of unknown origin or with a known history of heart failure with worsening dyspnea or other changes in their clinical status, evaluation of left ventricular function would be recommended [1]. Reassessment of left ventricular function in clinically stable patients with a known history of heart failure is not necessary, but may be considered if there has been no assessment within a year [1].

Noninvasive Cardiac Testing

Exercise stress testing is not useful for patients who are low risk undergoing a low-risk surgery [1]. For patients with elevated risk, that is, perioperative cardiac risk greater than 5%, and excellent (>10 METS) functional capacity, it is reasonable to forgo exercise testing and proceed to surgery [1]. It may also be reasonable to forgo exercise testing in those patients with elevated risk and moderate to good (>4 to <10 METS)

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functional capacity [1]. If a patient has an elevated surgical risk and an unknown functional capacity exercise stress testing prior to scheduled surgery would be reasonable if it will change management decisions [1]. Lastly in patients with elevated risk and unknown or poor functional capacity (<4 METS), it is reasonable to perform either exercise or pharmacological cardiac stress testing with imaging prior to the scheduled procedures to assess for the presence of myocardial ischemia [1].

Chest Radiography

In otherwise healthy individuals who do not display signs of respiratory illness, chest radiography (CXR) is not recommended for preoperative evaluation [6, 11]. In patients who are presenting for a preoperative evaluation and they display signs or symptoms of a new or unstable cardiopulmonary disease a CXR would be indicated prior to preoperative risk stratification [1, 6].

Pulmonary Function Testing

The role for pulmonary function tests in patients is undefined and unproven in those undergoing extra thoracic surgeries [2, 11]. Data does not suggest a prohibitive spirometric threshold below which the risks of surgery are unacceptable [9–11]. Screening pulmonary function tests with measurement of carbon monoxide diffusion capacity is universally utilized for risk stratification and predicting mortality in patients undergoing lung resection or reduction surgery [9–11].

Electrolytes

Basic electrolyte and renal function testing are not routinely needed but should be driven by medical condition and current medication use [2, 6]. Electrolyte testing should be implemented if a patient has a history of any of the following conditions: congestive heart failure, chronic kidney disease, hypertension, diabetes mellitus, or liver disease [2, 6]. Testing should also be performed if a patient is on certain medications which include diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, or digoxin [6].

Urine Analysis

Collection of preoperative urine analysis in patients has been shown to have very little predictive value in decreasing postoperative complications in asymptomatic patients [6]. Additionally, there is very little evidence that even an abnormal result leads to increased postoperative complications [6]. The general consensus is that routine urine analysis in asymptomatic patients is not recommended with the exception of the patients undergoing surgical implantation of foreign body (prosthetic joint or heart valve) or invasive urologic procedures [6]. A urine pregnancy test should be considered in all women of childbearing age [2].

Glucose Monitoring

Glucose testing should be considered in patients with signs and symptoms of undiagnosed diabetes, history of prolonged usage of glucocorticoids, or with a known history of poorly controlled diabetes [6]. General consensus states if a patient has well-controlled diabetes, routine preoperative glucose evaluation is not beneficial. In patients with known diabetes who display signs of poorly controlled diabetes, glucose evaluation with a random glucose or hemoglobin A1c may be beneficial if it would change perioperative management [3]. Short-term glucose management especially in the postoperative may decrease infection and complication rates [13].

Complete Blood Count

A complete blood count (CBC) has universally been part of the routine preoperative examination for many years, but this practice has been based on

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low level evidence or expert opinion [19]. Current consensus recommends preoperative CBC testing for patients who likely have an underlying anemia secondary to conditions such as chronic kidney disease, chronic liver disease, chronic inflammatory/autoimmune disorders, menstrual disorders, high risk for nutritional deficiencies, demonstrate signs/symptoms of chronic anemia, or undergoing a procedure in which significant blood loss is anticipated [2, 6, 19].

Coagulation Testing

Coagulation testing should be reserved for patients who have medical conditions associated with impaired hemostasis (liver disease, renal disease, diseases of hematopoiesis) or taking anticoagulants [6]. If history suggests problems with excessive bleeding, spontaneous bruising or a family history of a heritable coagulopathy appropriate coagulation testing should also be performed [2, 6].

Perioperative Medications

Beta Blockers

Continuation of beta blockers in the perioperative period has been well established for patients who are currently receiving long-term beta blocker therapy [20]. The benefit of initiating beta blocker therapy in the perioperative window is considered reasonable if a patient is determined to be intermediate or high risk for myocardial ischemia based on preoperative risk stratification testing [1]. It is also reasonable to initiate beta blocker therapy if a patient has three or more RCRI risk factors such as diabetes, heart failure, CAD, renal insufficiency, and CVA [1, 20]. Initiation of new beta blocker therapy in the perioperative window should be initiated in a time frame to allow the provider to assess the safety and effectiveness of the new medication [1]. Beta blocker therapy therefore should not be started on the same day as surgery [1, 20]. Perioperative beta blockade is most beneficial when initiated at least 1 week to 1 month preoperatively and continued for at least 1 month postoperatively [1, 20]. Therapy should be titrated to a resting heart rate of 55–70 beats per minute [20]. Chronic obstructive lung disease without severe reactive airway disease is not a clear contraindication for not initiating cardioselective beta blocker therapy in high-risk patients [20]. Resumption of beta blocker therapy postoperatively should be dictated by clinical circumstances and may need to be temporarily discontinued based on clinical factors such as hypovolemia, infection, significant blood loss, anemia, clinical instability, or other conditions that may complicate heart rate titration [1, 20].

Angiotensin-Converting Enzyme Inhibitor (ACE)/Angiotensin-Receptor Blockers (ARBs)

Due to their high utility in medicine, it is extremely common to encounter a patient on either an ACE or ARB. Guidelines suggest if a patient is currently stable on an ACE or ARB it is reasonable to continue these medications during the perioperative window [1, 20]. The most common adverse effect with their continuation is postoperative hypotension in those patients taking an ACE/ARB on the morning of surgery [20]. No change in postoperative cardiovascular outcomes including death, MI, stroke, or kidney failure has been noted in patients that continue to take their ACE/ARB in the perioperative period [1]. Clinical practice guidelines do support the continuation of ACE/ARB therapy when utilized in the treatment of heart failure or hypertension [1].

Statins

Statins should be continued in patients currently receiving chronic statin therapy. Perioperative initiation of statin therapy is reasonable in patients undergoing vascular surgery or those patients with clinical indications for initiating stain therapy who are undergoing high-risk noncardiac surgeries [20].

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Antiplatelet Medications

Antiplatelet therapy is used for both primary and secondary prevention of vascular complications. When preoperatively evaluating a patient it is important to understand the indication for the antiplatelet therapy when considering temporarily discontinuing the medication prior to the time of surgery. In cases where aspirin is used as primary prevention of stroke, MI, or CVA, this medication should be withheld 7–10 days prior to surgery to minimize postoperative bleeding complications [1, 20, 21]. Resumption of medication can begin once adequate hemostasis is confirmed and bleeding risk is deemed low. A reasonable approach would be 24 h after low bleeding risk procedures and at least 48–72 h after higher bleeding risk procedures [20, 22].

For patients with history of cerebral vascular disease, myocardial infarction, or peripheral vascular disease, aspirin therapy for secondary prevention should generally be continued through the perioperative period unless the patient is undergoing a procedure with a high bleeding risk (intracranial, spinal, posterior eye surgery, or transurethral prostatectomy) [20–22].

Patients with a history of coronary artery disease and placement of either a bare metal stent (BMS) or drug eluding stent (DES) elective surgery should be delayed until past the high-risk period for stent thrombosis. The risk for stent thrombosis is highest in the first 4–6 weeks post placement [20, 22]. Ideally patients should be continued on dual antiplatelet therapy for greater than 30 days following placement of a BMS and a minimum of 6 months, but ideally 1 year after placement of a DES before undergoing elective surgery [22]. However, if the risk of delaying surgery is greater than the risk of a major cardiac event, dual antiplatelet therapy should be maintained especially during the first 4–6 weeks post stent placement, unless bleeding risk is higher than the risk for an adverse cardiac event [1, 20, 22]. If surgery dictates discontinuation of the platelet receptor (P2Y) inhibitor, aspirin therapy should be maintained if possible and the P2Y inhibitor restarted as soon as possible after surgery [22].

Dual antiplatelet therapy should be continued for at least 12 months before undergoing elective surgery in any patient with a recent history of acute coronary syndrome (ACS) regardless of whether the ACS was treated with medical therapy alone, percutaneous coronary intervention, stent placement, or coronary artery bypass graft surgery [20, 22].

Within any scenario close communication and consensus between primary care provider, surgeon, cardiologist, anesthesiologist, and patient is essential for managing perioperative antiplatelet therapy and determining the best course of action for the patient [1, 20, 22].

Anticoagulation

Common indications for anticoagulation include atrial fibrillation, mechanical heart valve, and acute or recurrent deep vein thrombosis. Decisions regarding the continuation of anticoagulation therapy in the perioperative window can be complicated and often require a multidisciplinary approach. The perioperative management of patients on antithrombotic therapy should be based on an assessment of the patient's risk for thromboembolism and perioperative bleeding risk [18]. Addressing these issues will determine whether antithrombotic therapy is stopped prior to surgery and whether bridging therapy should be considered.

For patients who are scheduled for a minor surgery that have a lower risk of bleeding complications, such as cataract removal, minor dermatologic, or dental procedures, general recommendations would be to continue vitamin K antagonist (VKA) therapy in those scenarios [18]. Surgeries and procedures that carry an increased bleeding risk include: urologic, bowel resection, colonic polyp resection, joint arthroplasty, cancer surgery, surgeries involving highly vascular organs such as liver, spleen, kidney, implantable cardiac devices, intracranial, spinal, or cardiac [18]. Patients undergoing procedures with increased bleeding risk will need to have their VKA therapy stopped to reduce perioperative bleeding complications [18]. Once it is

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deemed necessary to halt VKA therapy, the VKA should be stopped 5 days prior to the planned surgery [1, 18]. Once the decision is made that VKA therapy should be halted, the patient's risk for thrombosis needs to be assessed to determine whether they will require bridging with LMWH or intravenous unfractionated heparin in the perioperative period. Risk stratification for thrombotic events in patients with atrial fibrillation is based on the CHADS 2 score, mechanical heart valve patients on the position and type of valve, and those with venous thrombosis on the time interval from the index embolus [18]. High-risk patients for thromboembolism include those with any mitral valve prosthesis, caged or tilting disc aortic valve, recent stroke or transient ischemic attack (TIA), atrial fibrillation with a CHADS2 score of 5 or 6, venous thromboembolism (VTE) with the last 3 months, or history of severe thrombophilia. These patients should receive bridging therapy with therapeutic doses of LMWH (Lovenox/enoxaparin 1 mg/kg bid or 1.5 mg/kg daily) [18]. Patients with atrial fibrillation and a CHADS2 score of 3–4, patients with a mechanic aortic valve and an additional risk factor such as atrial fibrillation or CHADS2 score above 1, and patients with a VTE in the last 3–12 months or non-severe thrombophilia are considered at moderate risk for thromboembolism and should be considered for bridging with LMWH based on surgery and individual patient factors [18]. Patients who are scheduled to undergo major cardiac surgery or carotid endarterectomy surgery are not candidates for bridging as the intraoperative bleeding risk is too high [18].

Resumption of VKA therapy in the postoperative window is dependent on surgeon preference as well as type of surgery. For most scenarios it is general practice to resume VKA therapy 24 h postoperatively, or when oral intake is tolerated [18]. Dose adjustments are dependent on postoperative medications as well as patients INR levels.

Novel oral anticoagulants (NOACs) are rapidly replacing VKA in the clinical setting; however, there is limited data to support a general consensus in their perioperative management [1]. As with the VKAs, perioperative management should be based on an assessment of the patient's risk for thromboembolism and perioperative bleeding risk. For procedures with a high risk of bleeding, or where hemostatic control is necessary, NOACs should be held 48–72 h prior to the scheduled procedure [1] (Table 6). For patients undergoing low-risk procedures who are also low risk for thromboembolism, discontinuation of NOACs can be as minimal as 24 h prior to procedure [1]. Resumption of NOACs in the perioperative window, depending on bleeding and thromboembolism risk, can be resumed between 24 and 48 h postoperative in most scenarios [1]. The rapid offset and onset of the NOACs may obviate the need for bridging anticoagulation.

Oral Hypoglycemic Agents

Preoperative evaluation of patients with diabetes should include their glycemic control history as well as the presence of any concomitant kidney disease, gastroparesis, or neuropathy which may lead to perioperative complications [23]. Patients with type 2 diabetes who take oral hypoglycemic drugs or noninsulin injectables are advised to

Table 6 NOAC discontinuation schedule [4]

Suggested Discontinuation Schedule for NOACs				
	Direct Thrombin Inhibitors (Dabigatran)		Factor Xa Inhibitors (Rivaroxaban, Apixiban, Edoxaban)	
Creatinine Clearance (mL/min)	Low Bleeding Risk	High Bleeding Risk	Low Bleeding Risk	High Bleeding Risk
≥80	≥1 day	≥2–3 days	≥1 day	≥2 days
50–80	≥1–2 days	≥3–4 days		≥2–3 days
30–49		≥4 days		≥3–4 days
15–29	Contraindicated	Contraindicated	≥36 h	≥4 days

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continue their usual routine of antidiabetic medications until the morning of surgery [23, 24]. On the morning of surgery, they should hold their oral hypoglycemic and noninsulin injectable drugs [23, 24]. The exception being long-acting sulfonylureas and sodium-glucose cotransporter-2 (SGLT-2) which should be held minimally 24 h prior to surgery [23, 25]. Generally the preoperative treatment regimen can be reinstated once the patient is eating well with the exception of Metformin (Glucophage) [23, 24]. Metformin has an increased risk of lactic acidosis in the perioperative window. Factors that can increase a patient's risk of developing lactic acidosis include: renal failure, administration of iodinated contrast, concomitant use of nephrotoxic medications (NSAIDs, ACE-I, diuretics), and severe left sided heart failure [24]. Due to this increased risk of lactic acidosis it is important to avoid resumption of metformin too early in the postoperative period; therefore it is recommended to wait at least 48 h after surgery to ensure the presence of adequate renal function before resuming this medication [23, 24].

Insulin

Type I diabetic patients are a subgroup in which glycemic agents should not be stopped in the perioperative window as their risk for diabetic ketoacidosis is much higher [24]. It is recommended for type 1 diabetic patients to remain on their basal insulin regimen through the perioperative period. During the preoperative evaluation it is important to include documentation of their basal regimen as well as their insulin correction factor [24]. If the patient uses an insulin pump, it is appropriate for them to continue their basal insulin and if needed bolus insulin can be administered as blood sugar levels necessitate [25]. In patients whose basal rate is calculated to keep the blood glucose in normal or low-normal ranges or when there is history of low glucose measures as an outpatient, patients may reduce the dose of long-acting basal insulin by 20–25% the evening before surgery to avoid any chance of preoperative hypoglycemia [25, 26]. If they routinely take basal insulin only in the morning, then the reduced dose should instead be administered on the morning of surgery [25]. Patients who are on twice daily basal insulin should reduce the dose by 20% to 25% in the evening prior to as well as the morning of surgery [25]. However, in patients who take high doses of basal insulin (>60% of total daily insulin) or total daily insulin dose is greater than 80 units or are at high risk of hypoglycemia (elderly, renal or hepatic insufficiency, prior hypoglycemic episodes); basal insulin dose should be reduced by 50% to 75% to minimize hypoglycemia risk [25]. During the fasting state, prandial insulin is held, and subcutaneous correctional insulin initiated with frequent blood glucose monitoring every 4 to 6 h [25].

Postoperative Monitoring

Despite proper preoperative risk stratification unfortunately 5% of patients will have a cardiac complication including death or nonfatal MI in the first 30 days following surgery [27]. Recent research is investigating additional preoperative and postoperative monitoring techniques beyond clinical risk calculators, which may be effective in helping to further mitigate postoperative cardiac complications. One such technique is laboratory measurement of brain natriuretic peptide (BNP) or N-Terminal fragment of proBNP (NT-proBNP) in the preoperative period to further identify patients at higher risk of cardiac complications.

The Canadian Cardiovascular Society has endorsed measurement of preoperative BNP levels in patients who are undergoing noncardiac surgery and are considered high risk. High-risk patients include those who are 65 or older, 45–64 years of age with significant cardiovascular disease, or patients who have a revised cardiac risk index >1 [27]. In the postoperative window, the highest risk time period for a myocardial infarction to occur is in the first 48–72 h following surgery when analgesic medications may mask cardiac ischemic pain. Patients identified as high risk should have a BNP drawn in the preoperative window. Guidelines by the Canadian

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Cardiovascular Society identified values as ≥300 ng/L for pro BNP and ≥92 ng/L for BNP as thresholds associated with increased risk of death or nonfatal MI in the 30-day postoperative window [27]. Patients who were found to have BNP levels above threshold values had a 21.8% risk of death or nonfatal MI compared to only 4.9% in those who value was below threshold [27]. High-risk patients received more intense monitoring in the immediate postoperative period such as continuous cardiac monitoring, EKG immediately after surgery while patient is still in the post-anesthesia care unit, higher level of care within the hospital, and daily troponin monitoring for 48–72 h [27]. In those patients who did suffer myocardial injury following a noncardiac surgery, the addition of aspirin and statin was shown to reduce the 30-day mortality in these patients [27]. Preoperative evaluation of BNP may allow providers to better predict patient perioperative cardiac risk; however, further research is needed before this laboratory monitoring is universally incorporated into surgical guidelines.

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Care of the Patient with Sexual Concerns

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Francesco Leanza and Andrea Maritato

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Care of the Patient with Sexual Concerns

Sex, sexuality, and sexual function are often topics that patients want to discuss with their primary care provider [1–5]. The overall prevalence of patients with sexual concerns is estimated at 30% for men and 30–40% in women both in the USA and abroad [1–3, 19, 21, 28, 30]. Sexual health is defined by the World Health Organization as a "state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and

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respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences" [6, 7]. Evaluating patients with concerns about their sexual health is important and should be patient-centered [1–3, 5, 6]. Most sexual concerns are easily treated within primary care without need for referral [1–3, 5, 6, 8].

Definition of Sexual Dysfunction

The criteria for sexual dysfunction differ depending on which consensus committee or professional organization is defining the dysfunction. In this chapter, the definitions used for sexual dysfunction are based on the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* published by the American Psychiatric Association. The newest version of the DSM, the fifth revision (DSM-52013), revealed major changes to the definitions of sexual dysfunction [6, 9, 10].

Two new categories were developed: female sexual interest and arousal disorder and genito-pelvic pain/penetration disorder. Female sexual interest/arousal disorder in the DSM-IV-TR would have included hypoactive sexual desire and arousal disorders. And genito-pelvic pain/penetration disorders would have included dyspareunia and vaginismus. Female orgasmic disorder remains as a distinct category, and sexual aversion disorder was removed as it is seldom used as a diagnosis and there is little research to support the diagnosis. In men, the definition for premature ejaculation was further clarified to include ejaculation within 1 min of penile entry. Male orgasmic disorder was renamed delayed ejaculation disorder, and male hypoactive sexual desire disorder became a distinct category for men. Erectile dysfunction remained the same [6, 9–11].

Approach to the Patient with Sexual Concerns

Much of the information that is relevant to sexual (dys)function can be collected in a thorough History and Physical (H&P), such as past medical and surgical histories (including obstetrical history in women), psychosocial history, medications, family history, and a review of systems [1, 2, 5, 8, 12–15, 19, 21, 28, 30].

The history will reveal much of the information needed to make a diagnosis of sexual dysfunction and its etiology. The goal of history taking for sexual dysfunction should be to determine if there are any medical or psychiatric conditions that are known to cause sexual dysfunction (Table 1). Other important aspects of the history are any medication side effects, including herbals, supplements, and over-the-counter medications (Table 2).

Sexual History Taking

The initial question many providers ask in the sexual history varies in syntax; however, the content is the same: "When you are sexually active is it with men, women or both." Typically, providers ask about sexually transmitted infection (STI) history and current risk and/or contraceptive management as appropriate depending on the patient's needs [1, 3, 12, 19, 21, 28, 30].

There are a number of validated questionnaires for sexual functioning. The Brief Sexual Symptom Checklist (BSSC), a self-reported questionnaire for men and women, is easily adapted to primary care. This tool can easily be administered prior to the visit or with the provider. The BSSC quickly allows the provider to hone in on areas of sexual functioning that are troubling their patients and follows the DSM criteria for sexual dysfunction [1–3, 14, 21].

The BSSC begins with asking about satisfaction with sexual functioning. If the patient feels that they *do not* have any issues with their sexual functioning, it is appropriate to stop asking questions about this topic. The BSSC continues with questions about the duration of the dissatisfaction with the patient's sexual functioning and then hones in on interest in sex, pain with sex, how distressing the problem is, and whether the patient would like to discuss the problem with their provider. It also specifically asks women about genital sensation, vaginal dryness, and trouble

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Table 1 Risk factors for sexual dysfunction [1, 2, 6, 12–17, 19, 21, 25, 27, 28, 30]

Age*	Neurologic disease:	Substance use:	Body image
Medical conditions:	Degenerative disease*	Tobacco (ED)*	Eating disorder ego-dystonic
Atherosclerotic risk factors*:	Spinal cord injury*	Alcoholism*	Sexuality
Obesity (ED)	Parkinson's	Drugs:	Gender dysphoria
Diabetes*	Dermatologic conditions:	Cocaine(ED)*	Women:
Hypertension	Psoriasis	Cannabis	Obstetrical complications
Hypercholesterolemia	Lichen sclerosus	Methamphetamine (ED)	Postpartum period
Coronary artery disease*	Genitourinary disease	Heroin (ED)	Breastfeeding
Peripheral vascular disease*	STI, HIV disease	Anabolic steroids	Vaginal prolapse
Stroke *	Pain with sex	Social-interpersonal:	PCOS
Endocrinopathies:	Surgical conditions:	Stress:	Menopause*
Thyroid disorders*	Genitourinary* pelvic*	Work	Men (ED):
Hypogonadism*	Spinal*	Financial	Pudendal nerve neuropathy long-distance cycling
Pituitary dysfunction	Vascular	Relational	Sedentary lifestyle
Adrenal dysfunction	Trauma	Sexual trauma* and violence	
Hypothalamic dysfunction	Injury	Social-cultural	
Rheumatologic disease	Psychological:	cultural beliefs	
Chronic renal failure	Depression*	Religious beliefs	
Cirrhosis	Bipolar	Low educational level	
COPD	Sleep disorders	Unrealistic expectations	
Cancer treatments:	Anxiety	Influence of media (internet)	
Chemotherapy*	Trauma		
Radiation*	Psychotic disorders		

*Causes with a greater prevalence of sexual dysfunction
(ED) condition associated with erectile dysfunction

Table 2 Medications with sexual side effects [1, 12, 14–16, 18–21, 25–28, 30, 32]

Global sexual dysfunction (SD):	**Women desire only:**	**Men global SD:**
SSRIs*(50% paroxetine worst)	Trazadone	Ketoconazole
Antiandrogens	Venlafaxine	Spironolactone (gynecomastia)
Women global SD:	Statins	**Erectile dysfunction:**
TCAs	Beta-blockers	Antipsychotics*
Barbiturates	Spironolactone	Antidepressants*
Lithium*	Methyldopa	Venlafaxine
Affect desire and arousal:	Danazol	Benzodiazepines
Benzodiazepines	GnRH agonists	Beta-blockers*
Clonidine	Contraceptives	Thiazide diuretics
Tamoxifen	Histamine 2 blockers	Opiates
GnRH analogues	Promotility agents	Antiretroviral
Ultralight contraceptive pills?	Indomethacin	Histamine 2 blockers (cimetidine)
Aromatase inhibiters	Ketoconazole	TCA
Chemotherapeutic agents	Phenytoin	Phenytoin
Affect desire and orgasm:	**Arousal only:**	Phenobarbital
Antipsychotics*	Anticholinergics	Lithium
Amphetamines	Antihistamines	Bromocriptine
Narcotics		Levodopa
Digoxin		Gemfibrozil
		Methotrexate
		5-alpha reductase inhibitors
		Corticosteroids

*Most commonly has sexual side effects

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achieving orgasm. In men it asks about problems with getting or maintaining an erection, whether the patient ejaculates too early or has delayed ejaculation or none at all with or without orgasm, and finally if the penis has an abnormal curvature when erect [1–3, 8, 14, 21].

Physical Exam

The history should guide the physical exam and may or may not uncover the specific root cause of the sexual dysfunction. The cardiovascular exam should look for risk factors associated with atherosclerotic disease and cardiovascular disease. This includes body mass index (BMI), blood pressure, peripheral pulses, and lower extremity changes associated with peripheral vascular disease such as skin changes, lack of hair and/or claudication, as well as edema. The focus of the neurological exam is to assess for peripheral neuropathy, spinal cord disease, or trauma. The musculoskeletal exam should focus on mobility and ability to participate in sexual activity. Patients should be assessed for thyroid disorders by palpating the thyroid [1, 2, 12, 14, 15, 17, 19, 21, 28, 30].

The genital exam in all patients should assess for normal genital development, secondary sex characteristics, and any signs of anal-genital infection. Lack of pubic hair can be a sign of low androgen levels in women and low testosterone in men. In females, the breast exam can reveal the presence of galactorrhea. In addition, the female patient should be assessed for vulvar abnormalities, evidence of vaginal atrophy, and trauma/surgical repair such as episiotomy repair and STIs. The clitoris should be inspected for abnormalities, included tethering as seen in lichen sclerosus [4, 21]. A speculum and bimanual exam may reveal cystocele, rectocele and/or uterine or anal prolapse, pelvic muscle tone both hyper- and hypotonicity associated with dyspareunia, as well as vaginismus and evidence of endometriosis such as a fixed, retroverted uterus [1, 2, 5, 14, 21, 28]. In men, the exam should focus on any abnormalities or infections; the testes should be assessed for size, atrophy, varicoceles, and epididymitis. And the patient should be asked about erections, abnormal curvature, or disorders of the foreskin such as phimosis. The penis should be inspected, looking for abnormalities. The foreskin, if present, should be inspected and retracted fully if possible. The rectal exam should be used to assess for tone and in men for any signs of prostatic disease [2, 8, 12, 15, 19, 30].

Labs and Other Testing

Laboratory testing should be directed by the H&P to look for specific medical conditions associated with sexual dysfunction. Any patient with a complaint of sexual dysfunction should be screened for diabetes with a glucose and if elevated a hemoglobin A1c, atherosclerotic disease with a lipid panel, and for endocrine disease with a thyroid-stimulating hormone (TSH). In men with erectile dysfunction or hypoactive sexual desire, a total testosterone level should be drawn, ideally a morning level. Imaging should be directed by H&P [1, 2, 12, 14, 15, 17, 19, 28, 30].

Approach to Diagnosing Sexual Dysfunction

According to the DSM-5, in order for the diagnosis of any type of sexual dysfunction disorder to be made, the condition must be present for at least 6 months. Within every disorder, it is important to ascertain if the sexual dysfunction is lifelong (primary) vs. acquired (secondary) and situational vs. generalized and the amount of distress it causes to the patient defined as mild, moderate, or severe [1, 9, 10, 18].

When diagnosing sexual dysfunction, it is critical to determine if the etiology is related to a root cause such as an underlying medical condition (s) or a psychosocial issue (see Table 1). The typical pattern of a medical cause is an older patient with gradual onset of symptoms (unless related to surgery or trauma), generalized dysfunction, consistent or progressive symptoms, normal desire, and underlying comorbidities [2, 12, 19, 28, 30]. The typical pattern of a psychosocial cause is a younger patient with acute onset

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of symptoms in a specific situation with intermittent symptoms and decreased desire with absent or minimal underlying medical conditions [2, 12, 19, 28, 30].

It is important to note that more than one type of sexual dysfunction can exist. For example, men may have both hypoactive sexual desire disorder with delayed ejaculation and erectile dysfunction, and women may have both sexual interest/arousal disorder with delayed orgasm and anorgasmia [1, 2, 12, 14, 17, 19, 28, 30].

The DSMV states that if sexual dysfunction exists in the absence of a secondary cause, then a true primary disorder exists. If the cause of sexual dysfunction is thought to be secondary to an illness or psychosocial condition, *treatment must be medically maximized* (Tables 1, 2, 3, and 4).

Treating Sexual Dysfunction: General Principles

The periodic health exam is an excellent time to speak to patients and educate them about their sexual health and functioning. For some patients it is helpful to discuss normal anatomy. Providers will often have the female patient look at their anatomy with a mirror. And in the case of men explaining normal responses and functions such as nocturnal emission and erections. Also, it is important to emphasize the breadth of a person's sexuality, like normalizing masturbation and same-sex attraction [1, 8, 12, 14, 16, 17, 19, 21, 28].

In patients diagnosed with sexual dysfunction, it is important to address habits such as tobacco use, excessive alcohol and cannabis use, and illicit drug use as they are well-known to contribute to sexual dysfunction [12, 14, 15, 18, 19, 21, 28, 30]. Poor sleep due to an underlying physical or mental health issue affects multiple areas of functioning as does stress at work or in relationships [1, 12, 14, 15, 17, 19, 21, 28, 30]. Being overweight can affect body image, and obesity is associated with erectile dysfunction [12, 15, 18, 28]. Patients should be encouraged to be physically active, as exercise is associated with increased sex drive and better sexual functioning [12, 15, 18, 19, 21, 28, 30].

Pointing out treatable underlying causes of sexual dysfunction is an excellent way to activate patients by using motivational interviewing. For men with ED who smoke, this maybe the "hook" to engage them in behavioral change. Providers should discuss sexual side effects of medications with patients prior to starting them and as part of follow-up once initiated. Adjustments to medications can be made either by changing class, dosing, or adding adjunctive therapies [1, 12, 14, 16, 18, 19, 21, 28, 30].

Therapy is a critical aspect of treatment for sexual dysfunction. Individual therapy can address a number of concerns for sexual dysfunction, including patients with a history of trauma, such as interpersonal violence in past or current relationships and/or sexual abuse. Refugees who have experienced sexual violence and torture should be referred appropriately. Modalities like cognitive behavioral therapy (CBT) can explore negative patterns of thinking about sex, sexual function, and reduce anxiety associated with sexual (dys)function. Couples therapy can explore specific concerns in the relationship, such as conflict and communication issues. Sex therapy can explore the dynamics in the relationship or in the individuals that are preventing the couple from sharing an erotic life together. Sensate focus is used to establish communication between partners that begins with non-sensual touch and progresses to sexual intercourse. Sensate focus is easily learned by primary care physicians and is within the domain of primary care [1, 8, 12–14, 16, 17, 19, 21, 28, 30].

Diagnosing and Treating Sexual Dysfunction in Women

Decreased desire and arousal are the most common sexual complaints in women. Up to 46% of women experience disordered desire and up to 21% disordered arousal with increasing prevalence in women as they age. Orgasmic dysfunction is most associated with medication side effects and is common in primary care with a prevalence of 5–42% and a prevalence of 4–7% in the general population. Pain with intercourse

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Table 3 Medical treatment of sexual dysfunction in women [1, 14, 16, 20–22, 28, 29, 34, 35, 36]

Female sexual interest/ arousal disorder	1. Postmenopausal women with only genitourinary syndrome of menopause (GSM) can be treated with vaginal estrogen (tablets, gels, cream, and rings equally effective). Lowest effective dose should be used. Duration of treatment has not been established. Usual treatment is daily dosing for several weeks and then enough use to maintain effect. Use with consultation in women with PMH of cancer 2. Postmenopausal women with GSM-related dyspareunia plus vasomotor symptoms can be treated with systemic estrogen. Women with an intact uterus must have progestin as well. Lowest effective dose should be used 3. Postmenopausal women with moderate to severe dyspareunia from GSM can use ospemifene (Osphena) or intravaginal DHEA prasterone (Intrarosa) (as an alternative to vaginal estrogen). *consultation GYN 4. Postmenopausal women with sexual interest/arousal disorder: Transdermal testosterone (not FDA approved in women) – Studies show 300mcg/day patch in women who are already on estrogen therapy. Studies show consistent improvement and least side effects at 300mcgs. Debate over dosing as this is superphysiologic. Some use of testosterone gel (this has not been studied but allows for lower dosing~1/5 to 1/10 of the dose for men). Treat for 3–6 months trial. Measure baseline testosterone and after 3–6 weeks of initial treatment. If ongoing, check levels every 6 months. If no benefit at 6 months, discontinue. There is no efficacy and safety data after 24 months. Suggest monitoring liver function and lipids. Intrinsa 300mcg/day (testosterone patch available in Europe). Side effects: Hirsutism (associated with dose, women not more likely to stop due to hair growth, acne (<10%), virilization rare, lower does mild), cv risk (risk not established). ACOG suggests women using should be "counseled about the potential risks and unknown long-term effects." *recommend initial evaluation with endocrinology or OB/GYN as off-label use and co-management 5. Small studies in women with both arousal and interest disorders showed improvement of genital sensation and satisfaction with foreplay and intercourse with sildenafil (Viagra) 25–100 mg daily. *recommend consultation. ACOG recommendation is to not use in the clinic setting.
Female orgasmic disorder	1. Testosterone for hypogonadism. Doses above 2. Antidepressant induced: Add bupropion SR 150 mg–300 mg daily (higher dose the better). *some studies show benefit for decreased libido in women without depression 3. Phosphodiesterase inhibitors (PDE5I) limited studies and mixed results. Studies showed promise in women with SSRI-induced orgasm disorder. Controversial to use. *recommend consultation
Genito-pelvic pain/ penetration disorder	1. Maximize medical treatment of underlying disorder 2. Vaginismus: Botox may improve symptoms (not well studied) 3. Vulvodynia: Overnight lidocaine ointment, amitriptyline, gabapentin (Neurontin), pregabalin (Lyrica), duloxetine (Cymbalta) 4. For treatment of GSM-related dyspareunia, see female sexual interest/arousal disorders
Other	Herbals: Not well studied. Limited data. Safety concerns 1. Maca extract may improve SSRI-induced sexual dysfunction 2. Lady Prelox (pine bark extract and other ingredients) may improve sexual function in women of reproductive age 3. *Tribulus terrestris* may increase sexual desire

often has an underlying cause and is frequently seen in the primary care setting with a prevalence of up to 46% in primary care and 3–18% in the general population [1, 14].

In 2013, atrophic vaginitis was renamed genitourinary syndrome of menopause (GSM) at a consensus conference between the International Society for the Study of Women's Sexual Health and the North American Menopause Society.

"GSM is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder. The syndrome may

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Table 4 Treatment of sexual dysfunction in men [8, 12, 15, 17–19, 23, 24, 30, 32, 37, 38]

Male hypoactive sexual desire disorder	Testosterone for hypogonadism: depo-testosterone (T) 200–250 mg every 2 weeks) Transdermal testosterone (closer to circadian levels) Patch applied to the arm, back, or upper buttocks alternate sites and avoid sun-exposed area as it can cause skin irritation (multiple formulations) Testosterone gel applied daily to clean dry skin over the shoulders, upper arms, or abdomen Wash hands after gel use. *In T replacement, monitor CBC, LFTS, and PSA Bupropion 150 mg–300 mg daily
Premature ejaculation	SSRIs Fluoxetine (Prozac) 5–40 mg/day Citalopram (Celexa) 20–40 mg/day Paroxetine (Paxil) 10–40 mg/day * 20 mg on demand 3–6 h before sex Sertraline (Zoloft) 25–200 mg/day * 50 mg on demand 3–8 h before sex Tricyclic antidepressants (TCAs) Clomipramine 12.5–50 mg daily * 25 mg on demand 3 to 24 h before sex
Delayed ejaculation	Almost always related to underlying cause. Also includes retrograde ejaculation
ED: First line	Phosphodiesterase inhibitors (PDE5I) (see Table 5) * requires periodic monitoring for efficacy, side effects, and change in medical conditions, including new medications
Second line	Medicated urethral system for erection (MUSE) (alprostadil). Self-administered. Primary care co-management with urologist. Needs plastic ring around penis and scrotum to maintain erection. Ring should not be in place for more than 30 min. Penile and scrotal pain common side effects. First dose in office due to low risk of hypotension and syncope. Female partners may report vaginal discomfort after ejaculation
Third line	Intracavernous injection therapy. Self-administered. Referral to urology
Other	Vacuum constriction device. Primary care. Effective, low cost. Needs plastic ring around penis and scrotum to maintain erection. Ring should not be in place for more than 30 min. Caution in patients on anticoagulation and antiplatelet therapies
Other	Herbals: Not recommended by AUA due to insufficient studies or safety concerns Yohimbine: Meta-analysis which shows efficacy of yohimbine over placebo. Dosing is daily but exact dosing unclear from studies Korean red ginseng: Two small studies outside the USA. Small sample sizes. Viable alternative before invasive measures, dose is 900–1000 mg tid Pine bark extract (Pycnogenol) may improve ED. limited data Maca extract may improve ED. limited data ED dietary supplements: Warning by FDA may have active PDE5I ingredients with the same precautions

include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections. Women may present with some or all of the signs and symptoms, which must be bothersome and should not be better accounted for by another diagnosis" [14, 31]. While the quality of research on medical treatments for sexual dysfunction in women has improved over the last decade, there still is a paucity of high-quality research. There is much more research on sexual dysfunction in men, specifically erectile dysfunction. Research on herbal remedies is lacking and plagued with small sample sizes and concerns for safety as these are not FDA regulated [1, 14, 19, 21, 28, 30, 32].

Female sexual interest/arousal disorder is diagnosed if the patient lacks or has significantly reduced sexual interest and/or arousal. Specific criteria for the disorder include no or minimal interest in sexual activity, no or minimal sexual/erotic thoughts or fantasies, lack of arousal or response to erotic cues either externally or internally, decreased sexual activity and/or not interested in sex even when initiated by a partner, minimal sexual excitement and/or pleasure during

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sexual activity in almost all or all sexual encounters, and/or minimal arousal or sensations genitally or otherwise with sexual activity [9].

Prior to menopause, it is recommended that the provider focus on psychosocial concerns like relationship issues, underlying medical or psychiatric disorders, and medication side effects, such as selective serotonin reuptake inhibitors (SSRIs) and oral contraceptive pills (OCPs) [14, 21, 28]. As women (and men) age, interest in sex, sexual activity, and frequency does often decline. The same follows for women (and men) in relationships over time and as such may not be distressing to the patient [1, 3, 4, 21, 28]. There are two new drugs that have been FDA approved for premenopausal women with hypoactive sexual desire disorder. Flibanserin (Addyi) is only available through a restricted program from the manufacturer and therefore requires consultation. It is for women without depression and must be used with caution when mixing with alcohol. The studies on this medication show mixed results with concerns about significant side effects [14, 21, 28]. The drug bremelanotide (Vyleesi) is the most recently FDA-approved medication to treat premenopausal women with sexual interest and arousal disorder. Research on this recently approved medication is still emerging and should only be prescribed with consultation [21, 28]. In a Cochrane review, supplementation with bupropion has been shown to improve symptoms of low desire and arousal in women (and men to a lesser degree), experiencing side effects from antidepressants; higher doses show better response. Switching patients to alternative antidepressants with fewer sexual side effects is another option. However, the studies have small numbers of patients and inconsistent methodologies [1, 14, 21, 28, 32].

In postmenopausal women, vaginal atrophy and lubrication issues are common and usually are secondary to GSM (see Table 3 for treatment details) [1,14, g]. Education about masturbation is important as a treatment for arousal disorders as well as orgasmic disorders. Using adjunctive aids, such as the Eros Clitoral Device, which is FDA approved, can improve arousal through direct stimulation [1, 14, 20]. Lubricants can be helpful when sex is painful due to vaginal dryness. As the FDA categorizes these products as cosmetic, there is a paucity of research that recommends one lubricant over another. Water- and silicone-based lubricants can be used with condoms. These products should be selected with patient preference in mind [14].

The focus of medical treatment is alleviating symptoms of GSM. The best evidence and greatest consensus support use of vaginal estrogen as first line [14, 21, 28]. There are second-line treatments that can be used as alternatives to vaginal estrogen for GSM. Women with dyspareunia related to GSM and vasomotor symptoms can be given low-dose systemic estrogen with or without progestin. Ospemifene, an oral medication, is a selective estrogen receptor modulator (SERM), which has been FDA approved for moderate to severe dyspareunia secondary to GSM in postmenopausal women. And prasterone (Intrarosa) which is vaginal dehydroepiandrosterone (DHEA) can also be used [14, 21, 28] (see Table 3 for details). Research has established that systemic DHEA is *not* useful in the treatment of sexual interest and arousal disorders in women [14, 21].

In women who have maximized estrogen therapy and are still experiencing symptoms of GSM, transdermal testosterone is a good adjunctive therapy. Results are promising with some caveats. Most studies are in postmenopausal women. In one study, three women developed breast cancer taking testosterone and estrogen, prompting the FDA to not approve transdermal testosterone due to lack of long-term safety data. However, in this study the increase was considered insignificant, as a result use is off label [14, 21]. ACOG suggests women using transdermal testosterone should be "counseled about the potential risks and unknown long-term effects" (14). The use of sildenafil (Viagra) for women in both interest and arousal disorder and orgasmic disorder is controversial; studies show contradictory results. ACOG suggests that sildenafil not be used outside of clinical trials. Clinical benefit remains unclear and therefore should be prescribed in consultation with an appropriate specialist [1, 14, 21, 28].

In women with *orgasmic disorder*, most or all of the patient's sexual activity must either have

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absent, infrequent, or delayed orgasms or markedly reduced intensity of orgasm [9]. Anorgasmia is frequently a medication side effect, particularly with psychiatric medications (SSRIs are infamous for causing delayed orgasm or no orgasm and decreasing sexual desire). Secondary causes are typically related to underlying neurologic causes, such as neuropathy (diabetes), prior trauma, and/or surgery. Women who have male partners with ED and/or premature ejaculation may have difficulty reaching orgasm [1, 4, 16]. Behavioral interventions include psychotherapy and sexual education about anatomy and masturbation, including direct vibratory stimulation of the clitoris as well as sexual positions that focus on maximize clitoral stimulation (coital alignment) [1, 14, 16, 28]. Medications include bupropion as a possibility for improvement of anorgasmia secondary to antidepressant use; this is supported by a Cochrane review that included men and women [1, 14, 28, 32] (see Table 3 for more detail).

Women with *genito-pelvic pain/penetration disorder* must have persistent or recurrent vaginal or pelvic pain with vaginal penetration or intercourse; marked fear of the pain before, during, or after penetration; and marked hypertonicity of the pelvic floor muscles during penetration [9].

Specific treatments for pain and penetration disorders are directed by underlying cause. Treat to the type of pain: superficial (Vulvodynia, dermatologic disease, STI, Vaginismus) v. deep (Endometriosis, post surgical/obstetrical complications, bladder, uterine, ovarian and intestinal disease) [14, 21, 28]. And consider other etiologies, such as GSM or neuropathy [11,421,28]. Behavioral techniques include non-penetrating pleasuring techniques, biofeedback, relaxation therapy, and desensitization exercises. In both vulvodynia and vaginismus, these modalities are often provided by a physical therapist with expertise in these treatments [1, 14, 21, 28].

In the case of vulvodynia, vaginal hygiene is important. Patients should only wash with water and wear 100% cotton underwear during the day and none at night. Acupuncture may decrease pain. Lidocaine 2% gel or lidocaine 5% ointment on a moist cotton ball placed into the vestibule at bedtime can alleviate pain. Transcutaneous electrical nerve stimulation (TENS) may help women with vestibulodynia. Tricyclic antidepressants (TCAs) and anticonvulsants are considered first-line therapy (see Table 3) [1, 14, 21, 22].

Diagnosing and Treating Sexual Dysfunction in Men

In primary care, erectile dysfunction is a common sexual complaint. In men age 40–50, the prevalence is 2%, and at age 60–70, this increases to 40–50%. At first intercourse, fear of ED is 20%, and actual erectile dysfunction that hinders penetration is 8% [9, 12, 15, 30]. Male hypoactive sexual desire increases as men age with a prevalence of 6% in men age 18–24 to 41% in men age 66–74. Prevalence of true premature ejaculation based on the new definition of ejaculation within 1 min of vaginal penetration is 1–3%. However, prevalence of premature ejaculation with the prior definition of prematurity not including a specific time was 20–30%, making this a common complaint that causes significant distress in men [23, 24]. Delayed ejaculation is most often associated with medication side effects and substances, such as SSRIs [9, 12, 15, 19, 30] (see Table 4).

Men with *erectile dysfunction* have significant difficulty in getting and maintaining an erection and/or have significant lessening of the quality of the erection in most or all instances of sexual activity [9, 12, 15, 19, 30]. The abridged International Index of Erectile Function 5-item questionnaire is a brief questionnaire that classifies erectile dysfunction on a scale of mild to severe and can be easily used in primary care [12, 18, 19, 30]. It is important to note that ED itself is a predictor of vascular disease in men. Providers should consider screening men with diagnosed ED for peripheral vascular disease and cardiovascular disease [12, 18, 19, 30]. In addition, questions about nocturnal erections, AM erections, and quality of erections with masturbation are important when distinguishing between a psychosocial etiology vs. an underlying organic cause [12, 15, 18, 19, 30].

Phosphodiesterase inhibitors (PDE5I) are first-line therapy for ED. They are equally effective in

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treating ED and vary in how quickly they work and in half-life. Initially designed for men with ED secondary to antidepressant side effects, diabetes mellitus, and spinal cord injury, PDE5Is are effective and safe in men with ED due to multiple disease states regardless of cause and severity. Side effects are typically mild with some caveats [12, 15, 18, 19, 30] (see Table 5). Patient-reported treatment failure should be evaluated for new underlying medical conditions, hormonal abnormalities, food and medication interactions, timing and frequency of dosing, alcohol use or other substances, relationship concerns, and adequate sexual stimulation. An adequate trial of one PDE5I is four to six attempts for an adequate erection at the maximum tolerated dose. After failure of one PDE5I, a trial of a second PDE5I is warranted. It is reasonable to try daily dosing of tadalafil (Cialis) after one to two failed trials, after which referral to urology would be appropriate [12, 15, 19, 30] (see Table 5 for dosing). Patients with ED and hypogonadism should be supplemented with testosterone and trialed on a PDE5I together. This should be co-managed with an endocrinologist (see Tables 4 and 5 for details of treatment). Statin monotherapy has insufficient data to be recommended as treatment for ED. Surgical options are considered last resort [12, 15, 18, 19, 30].

Men with *hypoactive sexual desire disorder* have consistent lack of sexual or erotic thoughts, fantasies, or desire for sexual activity [9]. This disorder is most commonly related to aging and poor medical condition. Other risk factors include medication side effects, mental illness, stress, low erotic thoughts, and history of sexual abuse [17, 19, 21, 30]. Hypogonadism can be a cause of erectile dysfunction as well as hypoactive arousal disorder and can improve with testosterone therapy. Other endocrine etiologies such as elevated prolactin should be investigated by MRI for pituitary adenoma and are treated with bromocriptine and if necessary surgery. These two disorders may be co-managed with an endocrinologist. Bupropion may improve symptoms of sexual functioning and desire in men as in women [1, 17–19, 30].

In *premature ejaculation*, ask the patient if they ejaculate within 1 min of vaginal penetration most or all the time and are unable to control or stop ejaculation and if this is before the patient would have liked to ejaculate (i.e., level of distress). It is important to note that premature ejaculation may occur in instances of non-vaginal intercourse. The DSM-5 makes the point of stating that specific duration criteria have not been established for non-vaginal penetration [8, 9, 23, 24]. In the case of patients that do not meet criteria for premature ejaculation yet have significant distress, it is recommended that they receive reassurance, education, and psychotherapy if indicated and be counseled on pause techniques with masturbation, such as the "pinch and squeeze" to delay ejaculation [8, 23, 24]. Patients with acquired premature ejaculation should use pause techniques and psychotherapy as first line followed by medications. Patients with lifelong premature ejaculation should start with both treatment modalities. Patients with premature ejaculation may also have ED along with depression and/or anxiety. These patients often have high levels of performance anxiety [8, 23, 24]. Condoms can decrease sensitivity [8, 23, 24].

The American Urological Association (AUA) recommends offering patients topical treatment or SSRIs as first-line therapy depending on physician judgment and patient preference [23]. Topical anesthetics such as EMLA cream (lidocaine 2.5%/prilocaine 2.5%) can be used 20–30 min before intercourse. The EMLA may result in numbness of the vaginal walls, and allergies to any "caine" products for either partner are a contraindication to topical treatment [8, 23, 24]. Antidepressants (SSRIs and TCAs) with delayed ejaculation as a side effect may be used daily or "on demand" prior to intercourse (see Table 4). SSRIs are better tolerated and are safer [8, 23, 24]. Both the International Society for Sexual Medicine and the AUA have evidence-based guidelines with slightly different dosing. Daily dosing is especially warranted in patients with comorbid mood disorders. The AUA recommends men under 18 and those with a history of bipolar disorder not be prescribed these medications [8, 23, 24]. PDE5s can be used safely in premature ejaculation with signs of erectile dysfunction. There is conflicting opinion about use of PDE5I in men

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Table 5 Phosphodiesterase inhibitors (PDE5I) [12, 15, 18, 19, 30]

PDE5I	Dosing	Side effects
Sildenafil (Viagra) Short acting: Tmax 1 h, 1/2 life 4 h	Range 25–100 mg/dose Starting dose 50 mg Take 1/2–4 h(s) before sex	Class effects High-fat meal can delay absorption Use lower dose if managing side effects from other medications
Vardenafil (Levitra) Short acting: Tmax 1 h, 1/2 life 4 h	Range 2.5–20 mg/dose Starting dose 10 mg Can take 2.5–5 mg daily or 10 mg prior to sexual intercourse Take 1/2–4 h(s) before sex	Class effects QT prolongation* High-fat meal can delay absorption Use lower dose if managing side effects from other medications
Avanafil (Stendra) Medium acting. Tmax 30–45 min, 1/2 life 5+ hours	Range 50–200 mg/dose Starting dose 100 mg 50 mg if concerned about drug interactions Take 30 min before sex. Can work as fast as 15 min	Class effects High-fat meal can delay absorption Use lower dose if managing side effects from other medications
Tadalafil (Cialis) Long acting: Tmax 2 h, 1/2 life 18 h	Range 2.5–20 mg/dose Starting dose 10 mg Can take 2.5–5 mg daily or 10 mg prior to sexual intercourse Take 1/2–12 h(s) before sex	Class effects Back pain Use lower dose if managing side effects from other medications
Class effects: Precautions	Side effects	Complications
Renal and liver disease require dose adjustment Use with caution in: >65 years old Liver failure Renal insufficiency BP < 90/50 Uncontrolled hypertension (BP > 170/100) Congestive heart failure Recent MI or stroke or arrhythmia (last 3–6 months) Unstable angina Retinitis pigmentosa	Most common: Headache (10–15%) Facial flushing (5–10%) Nasal congestion (5–10%) Dyspepsia(rare) Can lower blood pressure (rare) Back pain worse with Cialis **Contraindicated with nitrate therapy***** Acute myocardial infarctions no nitro 24–48 h if on PDE5I**	HIV protease inhibitors interactions Use with alpha-blockers can cause hypotension **interactions with multiple medications. Sudden loss of vision is a rare side effect. Known to cause non-arteritic anterior ischemic optic neuropathy (NAION) (RF for NAION are: 50+, cardiovascular disease, DM, HTN, tobacco use) (counsel patients to stop PDE5I if loss of vision and seek care immediately)** Sudden hearing loss with or without tinnitus, vertigo, dizziness*

with normal erectile function, as well as concerns about priapism [8, 23, 24]. There is limited evidence that surgical procedures work for premature ejaculation [8, 23, 24].

With *delayed ejaculation*, it is important to ask patients if they have significant difficulty with delayed, infrequent, or absent ejaculation [9]. The most common etiology is medication side effect (see Table 2). The treatment for delayed ejaculation is determining the cause as this is rarely a primary disorder [9]. Patients at risk for retrograde ejaculation should be evaluated for this condition [18].

In the case of *substance/medication-induced sexual dysfunction*, there must be a temporal association between the substance/medicine (either initiation or withdrawal) and the dysfunction with no other explanation. With substance-induced sexual dysfunction, cessation is the only treatment. With medications, adjustments can be made (see Table 2). The research regarding treatments for sexual dysfunction secondary to

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antidepressants, specifically SSRIs, is compelling. In men, the recommendation is to use PDE5Is, and in both sexes, the addition of bupropion (300 mg) at higher doses is the most studied and may improve sexual functioning. Other less studied options are waiting for drug tolerance (e.g., SSRIs usually 6 months), taking a drug holiday, adding bupropion to an SSRI regimen, or switching to medications with fewer sexual side effects (bupropion, mirtazapine, and most recently vortioxetine (Trintellix) show some promise, and further studies are needed) [1, 14, 21, 27, 28, 32, 33].

Referrals

Most diagnoses of sexual dysfunction can easily be made in the domain of primary care and referral made to mental health providers for supportive therapy as well as specialized physical therapists. Indications for specialized referral are treatment failures, contraindications to standard therapy, cases requiring surgical intervention, and patient request. Patients with complex endocrinopathies (adrenal, pituitary, hypothalamic), vascular and neurologic disease, or chronic persistent mental illness can be co-managed or referred depending on provider comfort and patient preference [2, 8, 18, 19, 30].

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Care of the Alcoholic Patient

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Overview

Alcohol, as an intoxicant, has been a part of human civilization for millennia. Alcohol's intoxicating effect appears to be due to the altering of cell membrane's action potentials, specifically modulating the activity of gamma aminobutyric acid (GABA) and *N*-methyl- d-aspartate (NMDA) channels. Enhancing GABA's inhibitory effect leads to a global decrease of membrane potentials. NMDA, an excitatory neurotransmitter, is blocked in the presence of ethyl alcohol. Acutely, this results in an anxiolytic effect and lowers inhibitions. Higher blood alcohol concentrations (BAC) lead to slurred speech, confusion, and motor impairment. Levels above 300 mg/dL (0.3 g/dL) can cause stupor, coma, respiratory depression, and finally death.

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Alcohol use disorder (AUD) is an intersection of multiple variables affecting all social and ethnic groups. Genetic predisposition, social variables, family issues, and comorbid medical/psychological diagnoses factor into the development of AUD [1].

Alcohol abuse causes cirrhosis and increases the risk of cancers of the head, neck, and digestive tract. Excess alcohol intake causes or exacerbates hypertension, cardiomyopathies, stroke, and dementia. Pancreatitis and pneumonia can be the result of alcohol misuse as can an array of psychiatric disorders and other substance abuse disorders.

Prevalence

During their lifetime, 20% of men and 10% of women will be diagnosed with AUD [1]. The risk of alcohol dependence is 12.5% over a patient's lifetime [2].

Adolescents and young adults have more binge drinking, defined as males drinking five or more drinks (four for women) at any one time. Patients exposed to alcohol at a young age are more likely to develop problematic drinking or other substance abuse problems [3].

The elderly are not immune to AUD with 2–4% suffering from alcohol abuse. In the older patient, more neurologic and physiologic impairment occurs at a lower BAC. Care should be taken when prescribing medications that can be potentiated with alcohol use, such as sedative-hypnotics.

Screening

The US Preventive Services Task Force (USPSTF) recommends screening adults aged 18 years or older for alcohol misuse and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse [4]. For patients between the ages of 12 and 17, the USPSTF believes the evidence is insufficient to assess the balance of benefits and harms of screening by a primary care physician. The USPSTF uses the term "unhealthy alcohol use" to define a spectrum of behaviors, from risky drinking to AUD. Risky drinking is consuming more than the recommend daily, weekly, or occasion amounts.

Alcohol use during pregnancy is one of the leading causes of preventable birth defects and developmental disabilities. The physician should screen for alcohol use at every prenatal visit. Screening benefits the mother, the fetus, and the society. Because there is no safe level of alcohol consumption during pregnancy, abstinence is recommended for the entire pregnancy.

The USPSTF recommends two tools for initially screening adults for alcohol misuse in the primary care setting: the abbreviated Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) and the single alcohol screening question (SASQ) method.

The AUDIT-C is comprised of the first 3 AUDIT questions and is scored from 0 to 12 points. Administering it takes between 1 and 2 min. A score of 5 or more for men (4 or more for women) is considered high risk for excessive and problematic alcohol use.

The SASQ method has the benefit of taking less than 1 min to administer. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommends this question, "How many times in the past year have you had 5 [for men] or 4 [for women and adults older than 65 years] or more drinks in a day?" A positive response warrants further investigation.

If a patient screens positive on a brief screening instrument, the provider should confirm unhealthy alcohol use with a longer instrument with greater specificity such as the Alcohol Use Disorders Identification Test (AUDIT) available at http://www.integration.samhsa.gov/AUDIT_screener_for_alcohol.pdf; AUDIT has ten questions and takes between 2 and 5 min to administer. The first three questions ask about the patient's consumption pattern. Questions 4–6 quantify the patient's tolerance or dependence on alcohol. The last four questions deal with alcohol-related problems the patient has experienced. A score of 8 or more has a high sensitivity and specificity for hazardous and harmful alcohol use.

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The CAGE questionnaire can be used for adolescents and adults, but it only detects alcohol dependence and not the full spectrum of unhealthy alcohol use. The four questions are: (1) Have you ever felt you should *Cut down* on your drinking? (2) Have people *annoyed* you by criticizing your drinking? (3) Have you ever felt bad or *guilty* about your drinking? (4) Have you ever had an *eye opener* or a drink in the morning to steady your nerves or to get rid of a hangover? A positive answer to two or more questions is sensitive and specific for AUD.

The CRAFFT questionnaire was designed for the adolescent patient [3]. If the answer to the first CRAFFT question is that they consume alcohol, then these additional questions are asked: Have you ever ridden in a *car* driven by someone (including yourself) who was "high" or had been using alcohol or drugs? Do you ever use alcohol or drugs to *relax*, feel better about yourself, or fit in? Do you ever use alcohol or drugs while you are by yourself, *alone*? Do you ever *forget* things you did while using alcohol or drugs? Do your family or *friends* ever tell you that you should cut down on your drinking or drug use? Have you ever gotten into *trouble* while you were using alcohol or drugs? If two or more of the questions are answered yes, there is the potential of a significant problem.

The USPSTF found no studies where screening for unhealthy alcohol use in any population leads to reduced unhealthy alcohol use; improved risky behaviors; or improved health, social, or legal outcomes [4].

Diagnosis

AUD diagnosis is a collection of physical and behavioral symptoms. The main features are alcohol craving, tolerance, and withdrawal. The diagnostic criteria are listed in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) (Table 1).

According to the DSM-5, remission of AUD is divided into three categories. Early remission is

Table 1 Definition of alcohol use disorder [5]

DSM-5[a]	
A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by **at least two** of the following, occurring within a 12-month period	
Alcohol is taken in larger amounts or over a longer period than was intended	Important social, occupational, or recreational activities are given up or reduced because of alcohol use
There is a persistent desire or unsuccessful efforts to cut down or control alcohol use	Recurrent alcohol use in situation in which it is physically hazardous
A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol
Craving or a strong desire or urge to use alcohol	Tolerance, as defined by either of the following: 1. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect 2. A markedly diminished effect with continued use of the same amount of alcohol
Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home	Withdrawal, as manifested by either of the following: 1. The characteristic withdrawal syndrome for alcohol 2. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms
Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol	

[a]*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition

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when no criteria (except for craving or strong desire) have been met for at least 3 months but less than 1 year. Sustained remission is achieved when no criteria (except for craving or strong desire) have been met for 1 year or longer. And remission in a controlled environment is a special circumstance used when a patient's access to alcohol is outside of their control.

Treatment of Alcohol Use Disorder

The provider's attitude toward the patient is an important aspect of AUD treatment. Alcoholism is a particularly stigmatized mental disorder [6]. These patients provoke more social rejection and negative emotions and are deemed responsible for their condition [6].

Patients with AUD feel embarrassed and deeply vulnerable regarding their prior consequences of alcohol abuse. However, patients who screen positive for alcohol abuse show motivation to change, especially as the severity of alcohol misuse increases. To assist the patient through this difficult time, the provider should be nonjudgmental in their approach. Focus the discussion on past problems that have occurred and take a supportive role in the patient's current problem indicating treatment can be successful.

Intermittent Abuse or Binge Drinking

For patients with intermittent alcohol abuse or binge drinking, the initial treatment is a brief intervention [7]. Brief interventions can be single or multiple short duration (5–25 min) feedback sessions regarding the patient's alcohol use. The healthcare provider discusses the consequences of the patient's alcohol use (i.e., failed relationships, accidental trauma, family stress, job loss), a safe alcohol intake amount, and assesses the patient's readiness for change. The patient is told their drinking is not medically safe and they should reduce their intake (Fig. 1). Patients who drink despite brief interventions are candidates for intensive therapy.

Chronic Alcohol Abuse and Dependence

Patients with moderate to severe AUD should be confronted about the negative consequences of their alcohol use. Strongly recommend they abstain and ask about their willingness to abstain (Fig. 2). Initial interventions can be cognitive behavioral therapy, 12-step facilitation, or motivational enhancement therapy. Advising patients to cut down or eliminate consumption has been equally effective at reducing alcohol intake.

At a minimum, patients can be referred to interactional group therapy or mutual help programs, such as Alcoholics Anonymous (AA). The time and location of the local AA meetings can be found during the patient's encounter, and the patient is strongly encouraged to attend a meeting that day.

Alcohol Withdrawal Syndrome

For patients who consume large quantities of alcohol (>20 drinks/week) for a prolonged period of time (>2 weeks) and discontinue intake, approximately 50% will experience withdrawal symptoms [2]. The symptoms begin 6–24 h after the last alcohol intake or a significant reduction in alcohol intake [8].

Alcohol withdrawal involves the central nervous system, autonomic nervous system, and cognitive function [9]. Alcohol withdrawal syndrome (AWS) is any two of the following: (1) autonomic hyperactivity (sweating, tachycardia); (2) increased hand tremor; (3) insomnia; (4) nausea or vomiting; (5) transient visual, tactile, auditory hallucinations, or illusions; (6) psychomotor agitation; (7) anxiety; or (8) tonic-clonic seizures [8]. Delirium tremens (DTs), a severe hyperadrenergic state (i.e., hyperthermia, diaphoresis, tachypnea, or tachycardia) characterized by disorientation, impaired attention, and consciousness with visual and/or auditory hallucinations, can occur with either no treatment or under treatment of AWS [8]. Delirium is characterized by fluctuating changes in the level of consciousness, cognition, and psychomotor activity [10].

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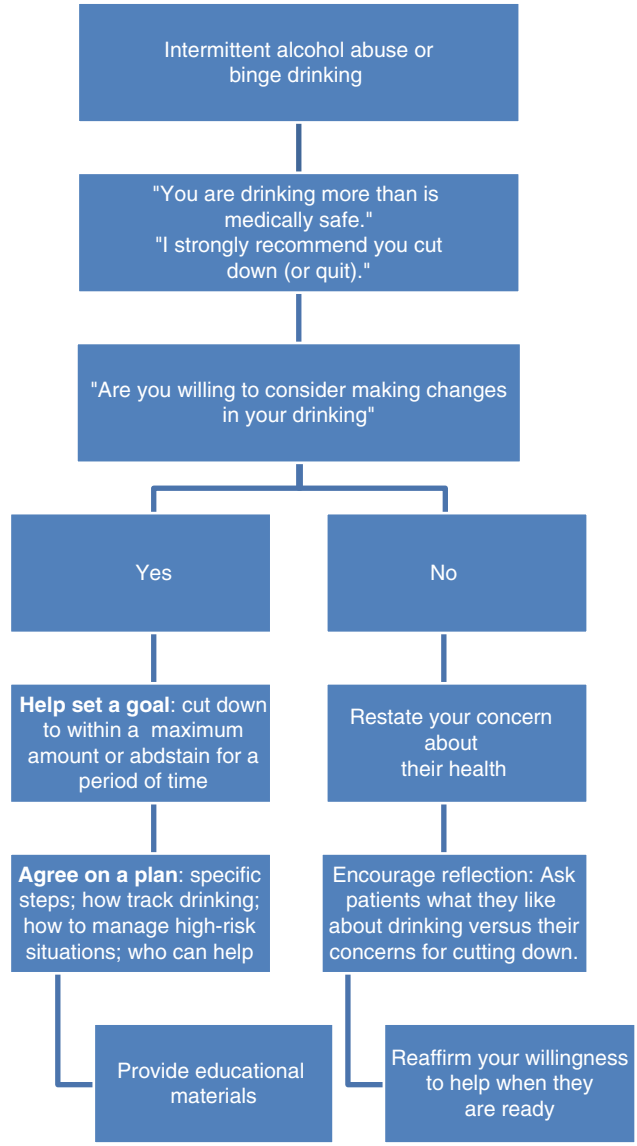


Fig. 1 Brief intervention for intermittent alcohol abuse or binge drinking http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide7.htm#top

AWS can be viewed in three stages. Stage 1 symptoms are mild anxiety, tremor, insomnia, headache, palpitations, or gastrointestinal disturbances with normal vital signs. Stage 2 symptoms are more intense and associated with abnormal vital signs (i.e., elevated BP or pulse, increased respirations, or increased temperature). Stage 3 includes stage 2 symptoms and either DTs or seizures. Progression to stage 2 or stage 3 can proceed quickly without treatment [11].

AWS severity is assessed using a validated instrument. The instrument often recommended is the Clinical Institute Withdrawal Assessment of Alcohol, Revised (CIWA-Ar) available at http://www.mdcalc.com/ciwa-ar-for-alcohol-withdrawal/ [12]. A CIWA-Ar score of 0–7 points is absent or very mild AWS, 8–15 points is moderate AWS, and $>$ 15 points is severe AWS [2]. The self-completed Short Alcohol Withdrawal Scale (SAWS) (available at http://www.aafp.org/afp/2013/1101/p589.html) has been validated in the outpatient setting [13]. A SAWS score $<$ 12 is mild AWS and $\geq$ 12 is moderate AWS.

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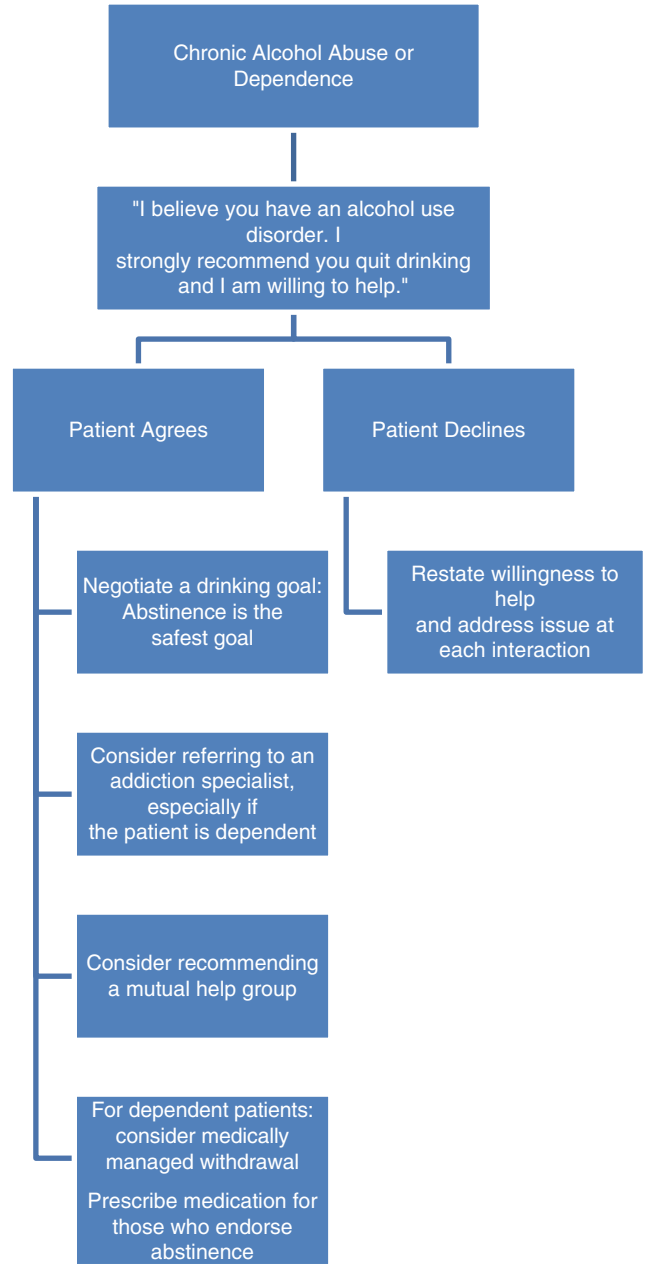


Fig. 2 Confronting chronic alcohol abuse or dependence http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide7.htm#top

Treatment of AWS

The AWS treatment goals are to reduce withdrawal symptoms, prevent complications (e.g., seizures, DTs, or death), and prepare the patient for long-term abstinence. Adequately and promptly abating AWS symptoms diminishes the severity of future withdrawal episodes and the risk the patient will resume drinking to ameliorate their symptoms [8]. Alcohol withdrawal seizures occur 24–72 h after the last alcohol intake, are typically tonic clonic, and last less than 5 min. Up to one third of patients with an alcohol withdrawal seizure will progress to DTs.

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When Is Medically Supervised AWS Treatment Not Necessary?

Patients with no alcohol intake in the preceding 5 days and have not abused other drugs do not require medical treatment. They should not be given medication, and any symptoms are related to comorbidities (i.e., anxiety, depression, other drug withdrawal) and not AWS.

Outpatient Treatment of AWS

Outpatient treatment of mild or moderate AWS is safe, effective, and less expensive than inpatient treatment [8]. Treating the patient in an outpatient setting can minimize expenses and allow for less interruption of work and family life. The following conditions preclude outpatient treatment: serious psychiatric conditions (e.g., suicidal, psychosis, etc.), acute illness, severe alcohol withdrawal symptoms, high risk of delirium tremens (DTs), history of withdrawal seizure, long-term intake of large amounts of alcohol, poorly controlled chronic medical conditions (e.g., diabetes, COPD, CHF), or lack of a support network [8].

While laboratory tests are not necessary for mild AWS, significant laboratory abnormalities would preclude outpatient treatment. A positive urine drug screen, signifying a co-occurring substance abuse, would prevent outpatient treatment.

And finally, in addition to medical and social issues that prevent outpatient treatment, the patient must be able to take oral medications, commit to frequent follow-up visits, and have a support person who can stay with them and administer medication [9]. The dispensing of medication requires clinical judgment and creates issues of control; thus caregivers must be informed of their role and be in agreement [8]. Family support can be critical in the success of outpatient treatment. However, family dysfunction or home alcohol consumption triggers can make outpatient treatment success unlikely.

Inpatient Treatment of AWS

AWS patients can be admitted to the hospital if they are not appropriate for outpatient treatment or if they fail outpatient treatment. AUD patients may be admitted to the hospital for other problems (e.g., pneumonia, pancreatitis, etc.) and then experience AWS. When patients are admitted, they become accessible to healthcare professionals for an intervention. If their reason for admission is the consequence of alcohol abuse, it could represent a triggering occurrence which could serve as a catalyst for change in alcohol use. For the nondependent patient, alcohol consumption was reduced if they had more than one brief intervention during their hospital stay. A single screening and brief intervention in the emergency room or nonemergency department hospital setting did not reduce alcohol consumption [14].

Reducing Symptoms

Alcohol withdrawal symptoms are increased with external stimulation. Patients should have a quiet and subdued environment with minimal opportunities for external stimulation. Patients with mild AWS may only require supportive care [8]. Most patients are given medication to reduce symptoms, particularly if there is any question about their duration of abstinence.

Because AWS patients are often nutritionally depleted, thiamine and folic acid supplementation are usually given to patients. Thiamine 100 mg orally once a day is recommended to reduce the risk of Wernicke's encephalopathy (i.e., oculomotor dysfunction, abnormal mentation, and ataxia). Folic acid 1 mg orally daily is recommended. Magnesium supplementation may be necessary but should not be a routine practice [9]. Intravenous fluids are not beneficial for AWS unless the patient has persistent vomiting or develops DTs.

Preventing Complications

Benzodiazepines (BZD) and anticonvulsants treat alcohol withdrawal symptoms and prevent complications (Table 2). They reduce psychomotor agitation and prevent progression of withdrawal symptoms [15]. They should be administered early in the AWS course. No evidence supports the superiority of any medication in treating AWS.

BZDs are long-acting (chlordiazepoxide, diazepam) or intermediate-acting (lorazepam, oxazepam). Long-acting BZD may be more efficacious in preventing delirium [16]. They have active metabolites that prolong their sedative and

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Table 2 Medications used to treat AWS [8]

Medication	Typical dosage	Common side effects	Contraindications
Benzodiazepines			
Chlordiazepoxide Diazepam Lorazepam Midazolam (for DTs)	25–50 mg 10 mg 2 mg 1–4 mg (IM/IV)	Sedation, fatigue, respiratory depression, retrograde amnesia, ataxia, dependence, and abuse	Hypersensitivity to drug/class ingredient Severe hepatic impairment Avoid abrupt withdrawal
Anticonvulsants			
Carbamazepine Oxcarbazepine Valproic acid Phenobarbital	600–800 mg 450–900 mg 1000–1200 mg 1500–2000 mg/day	Dizziness, ataxia, diplopia, nausea, vomiting	Hypersensitivity to drug/class ingredient, hypersensitivity to TCAs, no MAOI within 14 days, hepatic porphyria, avoid abrupt withdrawal
Beta-blocker			
Atenolol	50 mg if pulse 50–79 100 mg if pulse ≥80	Bradycardia, hypotension, fatigue, dizziness, cold extremities, depression	Hypersensitivity to drug/class ingredient, AV block second or third, uncompensated heart failure, cardiogenic shock, sick sinus syndrome without ICD, untreated pheochromocytoma, avoid abrupt withdrawal
Alpha-adrenergic agonist			
Clonidine	0.2 mg	Hypotension, dry mouth, dizziness, constipation, sedation	Hypersensitivity to drug/class ingredient, avoid abrupt withdrawal

anxiolytic effects [16]. Experts contend that long-acting BZDs provide a smoother withdrawal experience with fewer fluctuations in symptoms; however, intermediate-acting BZD have been used successfully [15]. In patients with hepatic dysfunction, the intermediate-acting agents (e.g., lorazepam, oxazepam) may be safer because they have no active metabolites. Chlordiazepoxide or oxazepam has less abuse potential, but no data supports their superiority in treating AWS. Because BDZ can cause fatalities when combined with alcohol, they should be prescribed in small amounts.

Carbamazepine and valproic acid are effective in treating AWS. However, anticonvulsant medication efficacy data is limited, and carbamazepine is associated with dizziness, ataxia, diplopia, nausea, and vomiting [17]. Limited evidence supports the use of valproic acid over BZD. Oxcarbazepine was as effective as carbamazepine in treating AWS, although one placebo-controlled randomized trial did not support that contention [18]. Gabapentin was effective in treating AWS and reducing drinking during withdrawal [19]. Anticonvulsant medications have reduced abuse liability, but they do not prevent withdrawal seizures or DTs.

Alternative AWS Medications: Less Effective

While baclofen was effective in reducing AWS symptoms and may reduce the risk of relapse without a risk of abuse, the overall data is mixed. As adjunctive therapy, beta-blockers and the alpha-adrenergic agonist clonidine are effective in reducing adrenergic symptoms but are not effective in preventing withdrawal seizures [15]. Neither phenothiazines nor barbiturates are recommended for AWS treatment in the outpatient setting [15]. Phenytoin is not effective in the treatment or prevention of alcohol withdrawal seizures.

Outpatient BZD Dosing Options

BZD are given in a fixed-dose or symptom-triggered schedule. A front-loading or loading-dose schedule is not recommended for outpatient treatment. The fixed-dose schedule utilizes a specific dosage at specific intervals regardless of the patient's symptoms. Additional

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medication is given if needed to control symptoms and the dosage reduced if overmedication occurs [8].

The symptom-triggered schedule utilizes medication when the patient has significant symptoms (i.e., CIWA-Ar > 9; SAWS ≥12). This schedule reduced medication use and shortened duration of treatment for inpatients [20]. However, one trial with a long-acting BZD in ambulatory patients revealed no difference between the fixed-dose and symptom-triggered schedule regarding total BZD dosage, patient satisfaction, or time to relapse [21]. Symptom-triggered schedules rely on the patient and caregiver to rate symptoms and may not be appropriate for some outpatients. A typical fixed-dose and symptom-triggered schedule is suggested (Table 3).

Inpatient Dosing Options

For hospitalized patients, BZDs can be given with a fixed-dose, symptom-triggered, or loading-dose regimen. For the hospitalized patient or the patient with DTs, a loading dose of a long-acting BZD has been found to improve outcomes in AWS [10]. The typical diazepam loading dosage is 20 mg every hour for 3–12 h until symptoms are controlled. Then either the fixed-dose or symptom-triggered outpatient regimen is implemented. Ethanol should not be used to treat AWS.

Monitoring Withdrawal: Outpatient

Most patients are evaluated daily until their symptoms decrease and the medication dosage is reduced. Blood pressure and pulse should be measured at each follow-up visit. If available, an alcohol breath analysis could be done randomly. Reassessment of the AWS severity is done with the same instrument used initially. When the CIWA-Ar is ≤8 or SAWS is <12, medication can be reduced and eventually discontinued. Alcohol withdrawal symptoms should resolve within 7 days of abstinence regardless of the severity of the AWS. The patient can be discharged to long-term outpatient treatment when symptoms are minimal, no medication is needed, and there has been no alcohol intake for at least 3 days. Patients who have an inadequate response to BZD, miss an outpatient appointment, or resume drinking should be referred to an addiction specialist.

Monitoring Withdrawal: Inpatient

For patients admitted to the hospital, the frequency of monitoring is every 4–6 h. If possible, allow patients to use normal clothes instead of hospital gowns. One advantage of inpatient treatment is the frequent interactions with the nursing staff, who can be supportive during treatment. The patient can be discharged when the AWS symptoms are mild.

Table 3 Fixed dosage and symptom-triggered dosage options to treat AWS [8]

Treatment day	Fixed dosage schedule (orally)	Symptom-triggered schedule (orally) For SAWS ≥ 12 or CIWA-Ar > 9
Day 1	Diazepam 10 mg every 6 h Chlordiazepoxide 25–50 mg every 6 h Lorazepam 2 mg every 8 h	Diazepam 10 mg every 4 h Chlordiazepoxide 25–50 mg every 4 h Lorazepam 2 mg every 6 h
Day 2	Diazepam 10 mg every 8 h Chlordiazepoxide 25–50 mg every 8 h Lorazepam 2 mg every 8 h	Diazepam 10 mg every 6 h Chlordiazepoxide 25–50 mg every 6 h Lorazepam 2 mg every 6 h
Day 3	Diazepam 10 mg every 12 h Chlordiazepoxide 25–50 mg every 12 h Lorazepam 1 mg every 8 h	Diazepam 10 mg every 6 h Chlordiazepoxide 25–50 mg every 6 h Lorazepam 1 mg every 8 h
Day 4	Diazepam 10 mg at bedtime Chlordiazepoxide 25–50 mg at bedtime Lorazepam 1 mg every 12 h	Diazepam 10 mg every 12 h Chlordiazepoxide 25–50 mg every 12 h Lorazepam 1 mg every 12 h
Day 5	Diazepam 10 mg at bedtime Chlordiazepoxide 25–50 mg at bedtime Lorazepam 1 mg at bedtime	Diazepam 10 mg every 12 h Chlordiazepoxide 25–50 mg every 6 h Lorazepam 1 mg every 12 h

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Management of DTs

DTs, severe AWS, is associated with an increased risk of death and a current mortality rate ranging from 1% to 4%. DTs symptoms begin about 2–3 days after initial withdrawal symptoms develop [10]. DTs risk factors include sustained heavy drinking, age over 30, more days since last drink, and, most importantly, a prior episode of DTs [8]. Hallucinations, common in DTs and primarily visual, are not dangerous but are distressing to the patient and his or her caregiver. Hallucinations were considered necessary for the diagnosis of DTs but that is no longer true.

The treatment of DTs is a medical emergency requiring inpatient care and prompt symptom treatment. The control of agitation is the initial goal and can be achieved with a benzodiazepine (Table 2). The patient's condition determines the route of administration. Most medications will be given intravenously, intermittently, until the symptoms subside. The doses required to control agitation vary dramatically and can be quite large (e.g., >2000 mg diazepam in the first 2 days) [2]. For these patients a front-loading dosage is preferred over fixed-dose or symptom-triggered regimen [10]. However, a Cochrane review did not find enough evidence of BZD effectiveness in treating patients with delirium not in the ICU setting. The available evidence did not support the routine use of BZD for delirium in the non-ICU setting [22]. Monitoring is more frequent than either outpatient or regular inpatient care, usually every 2 h. Confusion may be reduced by limiting stimulation, good lighting, and environmental cues such as having a clock or calendar visible.

Physical restraints may be used to protect the patient and staff utilizing the institution's restraint protocol. For patients who do not respond to high doses of a benzodiazepine, phenobarbital (60 mg IV q15min) or propofol (0.3–1.25 mg/kg/h IV) can be administered in the ICU [2]. Another ICU medication is dexmedetomidine (Precedex ®) (0.4–0.7 mcg/kg/h IV); an α_2-adrenergic agonist has been administered [23]. Intravenous fluids should be utilized to maintain hydration and to treat electrolyte abnormalities [10].

To reduce the risk of Wernicke encephalopathy (WE), all patients with DTs are given supplemental thiamine. The usual dosage is 500 mg intravenously infused over 30 min 1–2 times a day. Intravenous dextrose is to be avoided until after thiamine replacement. If dextrose is administered before thiamine, it might precipitate WE.

Long-Term Management of Alcohol Dependence

Due to the chronic and relapsing nature of alcohol dependence, implementing long-term treatment is essential for the maintenance of remission. From 40% to 60% of AUD, patients relapse within 1 year after entering treatment. Following recovery from alcohol withdrawal, continuing care can be provided in an inpatient or outpatient setting.

Interventions to maintain remission are based on the patient's current clinical status, medical and psychiatric comorbid conditions, level of current use, risk for relapse, motivation for recovery, and personal preferences [24]. The American Society of Addiction Medicine (ASAM) treatment criteria for addictive, substance-related, and co-occurring conditions (available at ASAMCriteria.org) can assist clinicians in determining appropriate levels of care. Levels of care include residential programs, partial hospital programs, intensive outpatient programs, and outpatient care [25].

Levels of Care

Residential care programs are inpatient programs providing housing, peer and professional support, and an alcohol-free environment. Examples of residential treatment models include community residential treatment facilities, therapeutic communities, and Oxford House [25].

Therapeutic communities provide comprehensive care and emphasize graduated personal and social responsibility. Appropriate patients for residential care tend to be relapse prone, poly-substance abusers, often with psychiatric comorbidities and poor social support. Staff and clients reside together and interact in activities

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with the goals of assimilation of social norms, development of social skills, and positive impact upon attitudes, perceptions, and behaviors. Typically, stays range from 18 to 24 months with a desired minimum of 90 days.

Oxford House (www.oxfordhouse.org) is a publicly supported recovery concept where individuals live together in democratically run, self-supporting residences without addiction counselors. The residential complement ranges from 6 to 15 individuals per house, and specific residences may be designated for men, women, or women with children. Treatment interventions are self-selected by the participants.

Partial hospital programs (PHPs) allow for increased flexibility for the patient who wishes to stay at home but needs a higher level of care. Patients participate a minimum of 20 h per week but can be as much as 6 h per day 5–7 days per week. The care includes individual and group counseling, medication management, didactic sessions, and even specialized services such as occupational therapy.

Intensive outpatient programs (IOPs) are structured similar to PHPs and may be housed in the same facility as a PHP but provide only 10–20 h of treatment per week. *Outpatient care* model utilizes similar services as IOPs, but interventions are less frequent (less than 10 h/week) and shorter in duration.

Psychosocial and Behavioral Interventions

Interactional Group Psychotherapy or "self-help" groups based on the 12-step program are historically significant, but evidence supporting their effectiveness is limited. The most well-known adaptation, *Alcoholics Anonymous* (AA), was founded in 1935 and thrives today as a worldwide network [26]. The 12 steps serve as a template for behavioral interventions aimed at maintenance of sobriety, and the fellowship provides an abstinent social network to replace lost "drinking buddies." Daily meetings are offered in a wide variety of venues, and group composition varies by age, gender, and interests of the participants. Common elements include the acknowledgment of individual powerlessness over alcohol and the existence of a higher power, selection of a sober sponsor, and an emphasis on relapse forgiveness. Companion organizations for family support include *Al-Anon* and *Alateen*.

For patients uncomfortable with the spiritual aspect of the model, similar nonreligious programs exist such as *SMART Recovery*, *Rational Recovery*, and *Save Our Selves*. Though the efficacy of AA has not been sufficiently assessed in randomized controlled trials, experts generally agree that it produces positive outcomes [27]. However, a Cochrane review concluded there is a lack of experimental evidence supporting the effectiveness of 12-step programs for alcohol dependence [28].

Group therapy is a formal continuing care therapy session led by a trained professional. Sessions typically last 90 min and occur one or two times per week. They may occur in a 12-step format where patients report on their progress through the steps and they are given feedback and support, or they utilize an instructional format which utilizes elements of cognitive behavioral therapy (discussed below) or emphasize skills development. The methods are equally efficacious and more cost-effective than individual therapy. Advantages include peer influence on sobriety, role modeling of sober behavior, avoidance of social isolation, and reinforcement by example that successful remission is possible.

Individual therapy occurs in sessions typically lasting 30–60 min. The frequency and duration of such sessions are dependent on the patient's duration of remission and on continued sobriety. Initially, clinicians may interact with patients three or more times per week. Care is stepped up or down based on the patient's progress.

Cognitive behavioral therapy (CBT) is a format which identifies triggers for alcohol abuse, develops coping strategies for risky situations, and defines alternative activities to replace those activities which challenge sobriety. Patients are given homework assignments to guide them in determining what leads to alcohol use and in developing responses to avoid relapse. A meta-analysis concluded that CBT was modestly beneficial in maintenance of sobriety [29].

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Relapse prevention is a form of CBT specifically aimed at identifying individual risk factors for relapse and then selecting and rehearsing coping responses for those risks. A meta-analysis demonstrated effectiveness comparable with other psychosocial interventions [30].

Motivational enhancement therapy (MET) is based on the premise that responsibility and capacity for change lay within the client. Motivational interviewing techniques include open-ended questions and affirmations, reflective listening, summarizing, and eliciting "change talk." The therapist emphasizes personal responsibility, and together, the therapist and client explore the risks of continued drinking, the benefits of abstinence, the treatment options, and the strategies for relapse avoidance.

Combined behavioral intervention is a specialized technique that incorporates components of CBT, interactional psychotherapy, and MIT.

Recovering patients benefit from therapy designed for couples and families. *Couple-based therapy* engages the client's spouse or partner with improving patient participation and positively influencing the patient's behavior toward sustained abstinence. *Behavioral marital therapy* (BMT) addresses issues of marital discord by education in improved communication, conflict recognition and resolution, and engagement of the couple in shared activities. A meta-analysis concluded that behavioral couple's therapy was superior to individual therapy.

Pharmacologic Interventions

Less than 10% of patients with AUD receive medications to assist in maintaining sobriety [31]. Three medications are approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence: naltrexone (oral and injectable), acamprosate, and disulfiram [31]. Acamprosate and oral naltrexone are effective in reducing a return to drinking, although no studies demonstrate superiority of one over the other [31] (Table 4).

No treatment is approved for adolescents younger than 18 years with AUD [32].

Naltrexone

Naltrexone, available in oral (*ReVia*) and injectable formulation, has proven efficacy in reduction of alcohol consumption [33, 34]. The oral form (50–100 mg per day) may be started prior to the cessation of drinking. Naltrexone antagonizes various opioid receptors negating the reinforcing effects of alcohol [31]. Common side effects include fatigue, nausea, vomiting, abdominal pain, headache, and dizziness and should be avoided in patients with active liver disease or on opioids. Injectable naltrexone in depot form (*Vivitrol*) was developed to increase compliance while minimizing side effects [32]. Adverse effects are similar to the oral formulation with the addition of injection site reactions and interstitial or eosinophilic pneumonia [35].

Acamprosate

Acamprosate (*Campral*) is hypothesized to exert effects on both glutamate and GABA; however, its mechanism of action is not clearly elucidated. The usual dosage is 666 mg three times daily after abstinence is achieved. Several meta-analyses support its efficacy in increasing abstinence [36]. However, the *COMBINE* study comparing the efficacy of acamprosate, naltrexone, and placebo found acamprosate to be no more effective than placebo. Patients with impaired hepatic dysfunction can use acamprosate but should be avoided in patients with severe renal dysfunction [32]. Though well tolerated, common side effects include diarrhea, insomnia, anxiety, depression, nausea, and dizziness [31].

Disulfiram

Unlike the other agents, disulfiram (*Antabuse*) does not act at the level of the neurotransmitter. Disulfiram inhibits acetaldehyde dehydrogenase, thus resulting in the accumulation acetaldehyde. Excess acetaldehyde produces a constellation of distasteful symptoms including nausea, vomiting, sweating, headache, dyspnea, flushing, and palpitations thus promoting an aversion to alcohol [31]. Dosages range from 125 to 500 mg daily. A meta-analysis did not find clinically significant benefit of disulfiram over placebo. Noncompliance was a major obstacle in the trials reviewed. A study with

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Table 4 Medication for long-term treatment of alcohol dependence

Medication	Dose	FDA approved	Mechanism of action	Side effects	Caveats
Naltrexone oral (*ReVia*)	50–100 mg QD	Yes	Opioid antagonist	Dizziness, nausea and vomiting, headache, and transient transaminitis	Avoid in acute hepatitis, hepatic failure, or with concurrent opioid use Monitor LFTs Can be started while drinking
Naltrexone injectable (*Vivitrol)*	380 mg q 4 weeks IM	Yes	Opioid antagonist	Dizziness, nausea and vomiting, headaches Anorexia, interstitial or eosinophilic pneumonia, and injections site reactions (cellulitis, induration, hematoma)	Avoid in acute hepatitis, hepatic failure or with concurrent opioid use Monitor LFTs Cannot start until abstinence is established
Nalmefene (*Selincro*)	20–80 mg QD	No	Opioid antagonist	Dizziness, headache, insomnia nausea and vomiting, tachycardia	Increases compliance with treatment
Acamprosate (*Campral)*	666 mg TID	Yes	Glutamate/ GABA receptors/ NDMA receptor	Transient diarrhea Vomiting Nervousness Fatigue	Avoid use in renal failure Cannot start until abstinence is established
Disulfiram (*Antabuse*)	125–500 mg Usually 500 mg for 1–2 weeks and then 250 mg QD	Yes	Inhibits acetaldehyde dehydrogenase	Fatigue, headache, rash, hepatitis, psychosis	Avoid alcohol containing products such as mouthwash for at least 2 weeks after stopping Do not use in pregnancy Monitor LFTs Contraindicated in patients with psychosis/severe CAD Effective when administration is supervised Cannot start until abstinence is established
Topiramate (*Topamax*)	50–300 mg Q day	No	Antagonizes glutamate/ GABA receptors agonist	Cognitive dysfunction, paresthesias and taste abnormalities, weight loss headache, fatigue, dizziness	Dose must be gradually increased and decreased
Gabapentin (*Neurontin*)	900–1800 mg QD	No	GABA mediated	Sedation at higher doses, dizziness, and abuse potential	
Baclofen	30 mg QD High dose 150–400 mg QD	No	GABA receptors agonist	Nausea, vertigo/dizziness, depression, sleepiness, abdominal pain, ataxia, and insomnia	Can be used in patients with liver disease

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Table 4 (continued)

Medication	Dose	FDA approved	Mechanism of action	Side effects	Caveats
Selective serotonin reuptake inhibitors	Various	No	Serotonin mediated	Depends upon drug chosen	Use in comorbid depression More effective in late-onset alcoholism

supervised medication administration demonstrated superiority of disulfiram over acamprosate and naltrexone in reducing heavy drinking days and average weekly alcohol consumption. Additionally, the time to first drink was increased with witnessed consumption of disulfiram. Once the supervisory component was removed, the benefit dissipated.

Other Agents

Topiramate (*Topamax*) is not an FDA-approved treatment for alcohol dependence but has demonstrated moderate effectiveness in the reduction of alcohol use in dependent patients [37]. Mitigation of alcohol consumption is believed to be mediated by effects on glutamate and GABA receptors. A meta-analysis showed decreased consumption of alcohol when compared with placebo. Common side effects include dizziness, somnolence weight loss, fatigue, nervousness, and cognitive dysfunction [31].

Gabapentin (*Neurontin*) has proven efficacy in dosages of 900 or 1800 mg daily versus placebo [38]. Side effects are dizziness and sedation which are dose-dependent. One study found gabapentin was most effective in preventing relapse to heavy drinking and promoting abstinence when the patient had more severe AWS [39]. Baclofen results were mixed in clinical trials compared with placebo at both low (30–60 mg) and high (150–400) doses. Though generally well tolerated, adverse effects included dizziness, depression, headache, paresthesias, ataxia, and insomnia [40]. Selective serotonin reuptake inhibitors (SSRIs) have only been found to be effective in the management of alcohol dependence in patients with a comorbid depression diagnosis [41].

Ondansetron may reduce alcohol consumption in patients with AUD when combined with CBI [42]. The effect may be due to the serotonin-3 antagonist effect. The studied ondansetron dosages were 4–16 mcg/kg twice per day.

Other Interventions

Acupuncture has been an accepted adjuvant therapy for many decades. Experts agree that it is most effective when combined with psychosocial and pharmacological interventions [43].

Hypnosis was used to treat addiction in the late nineteenth century with some success. Hypnosis studies are very limited and the numbers of participants small. One study reported a 77% success rate in 18 clients treated intensively (20 daily sessions) with sustained benefit at 1 year follow-up, while another study using audiotapes for self-hypnosis demonstrated improvement in self-esteem and serenity and a reduction in anger and impulsivity [44].

Intervention for sleep disturbances may benefit patients in maintaining sobriety as some patients use alcohol for its sedative effects. Promotions of good sleep hygiene, bright light therapy, and meditation are options (Table 5).

Emerging Interventions

Theoretically, the most successful interventions in the management of alcoholism should be those that are most adaptable and accessible for the needs of a broad spectrum of patients. Recent studies have explored modalities which utilize modern technology to interact and monitor patients following inpatient or intensive outpatient therapy. Technologies such as e-mailing, text messaging, Internet-based social support, Internet-based cognitive behavioral therapy applications, and telephone-based counseling are being used to facilitate maintenance of sobriety. Some research of Internet- and telephone-based models have proven benefit especially for CBT [45]. However, further adequately powered

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Table 5 Pharmacologic interventions in chronic alcoholism

Medication	Dose	FDA indication/	Mechanism of action	Side Effects	Cost	Caveats
Naltrexone oral (*ReVia*)	50–100 mg QD	Yes	Opioid antagonist	Dizziness, nausea and vomiting, headache, and transient transaminitis	$	Avoid use in acute hepatitis, hepatic failure or with concurrent opioid use Monitor LFTs Can be started while drinking
Naltrexone injectable (*Vivitrol)*	380 mg q 4 weeks IM	Yes	Opioid antagonist	Dizziness, nausea and vomiting, headaches Anorexia, interstitial or eosinophilic pneumonia, and injections site reactions (cellulitis, induration, hematoma)		Avoid use in acute hepatitis, hepatic failure, or with concurrent opioid use Monitor LFTs Cannot start until abstinence is established
Nalmefene (*Selincro*)	20–80 mg QD	No	Opioid antagonist	Dizziness, headache, insomnia, nausea and vomiting, tachycardia		Increases compliance with treatment
Acamprosate (*Campral)*	666 mg TID	Yes	Glutamate/ GABA receptors/ NDMA receptor	Transient diarrhea Vomiting Nervousness Fatigue		Avoid use in renal failure Cannot start until abstinence is established
Disulfiram (*Antabuse*)	125–500 mg Usually 500 mg for 1–2 weeks and then 250 mg QD	Yes	Inhibits acetaldehyde dehydrogenase	Fatigue, headache, rash, hepatitis, psychosis		Avoid alcohol containing products such as mouthwash for at least 2 weeks after stopping Do not use in pregnancy Monitor LFTs Contraindicated in patients with psychosis/severe CAD Effective when administration is supervised Cannot start until abstinence is established
Topiramate (*Topamax*)	50–300 mg Q day	No	Antagonizes glutamate/ GABA receptors agonist	Cognitive dysfunction paresthesias and taste abnormalities, weight loss, headache, fatigue, dizziness		Dose must be gradually increased and decreased
Gabapentin (*Neurontin*)	900–1800 mg QD	No	GABA mediated	Sedation at higher doses, dizziness, and abuse potential		
Baclofen	30 mg QD High dose	No		Nausea, vertigo/ dizziness, depression,		

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Table 5 (continued)

Medication	Dose	FDA indication/	Mechanism of action	Side Effects	Cost	Caveats
	150–400 mg QD		GABA receptors agonist	sleepiness, abdominal pain, ataxia, and insomnia		Can be used in patients with liver disease
Selective serotonin reuptake inhibitors	Various	No	Serotonin mediated	Depends upon drug chosen		Use in comorbid depression More effective in late-onset alcoholism
Ondansetron	4 mcg/kg BID	No	5 HT3 receptor antagonist	Diarrhea, prolonged QT, headache		Use in early onset alcoholism Avoid use in prolonged QT or with drugs that prolong QT

randomized-controlled trials are needed to determine the efficacy of these interventions. Additionally, how these interventions can best be incorporated into a comprehensive continuing care model for the long-term management of alcoholism must be explored.

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Care of the Patient with Chronic Pain

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Faraz Ghoddusi and Kelly Bossenbroek Fedoriw

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Definition and Scope of Chronic Pain

Chronic pain is pain that persists beyond the typical healing time of 3–6 months. The National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) estimate that over 50 million people in the United States suffer from chronic non-cancer pain (CNCP), which ends up being more than 20% of the population [1]. The annual healthcare costs for patients with CNCP are estimated at $560 billion, but despite the high prevalence, CNCP remains undertreated

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[2]. However, with the surge in public awareness and multiple national endeavors, including CDC updates on prescribing recommendations, there has been a significant drop in opioid prescription, with the Medical Expenditure Panel Surveys indicating that annual share of US adults who were prescribed opioids declined from 12.9% in 2014 to 10.3% in 2016. With the push to reduce opioid use and increase non-pharmaceutical therapies, primary care physicians have had been adjusting prescribing practices to align with updated best practices.

Patients with CNCP frequently are seen in primary care offices where their treatment is often coordinated by a family physician. While these patients and their pain can often be seen as challenging to manage, using a stepwise approach and collaborative care model can safely and successfully mitigate pain and improve function.

Treating Acute Pain

Acute pain tends to have an easily identifiable cause and typically resolves when the inciting injury heals. Non-opioid medications should be considered first line for acute pain; however, if opioids are indicated for an acute injury, providers must discuss the risks of treatment as well as the expectations for healing and engage the patient in mutual decision-making [3]. The transition from acute pain to chronic pain is not always obvious and providers can easily find themselves refilling opioid prescriptions long after the acute injury should have healed and without having discussed the risks of long-term opioids with patients. The CDC and NIH recommend that if opioid use is indicated, clinicians should prescribe the lowest effective dose and prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioid pain relievers (3 or fewer days will usually be sufficient) [4]. However, as with all symptoms, the key to acute pain management is evaluation and treatment of the underlying diagnosis.

Patient Assessment

Every patient in pain requires a thorough initial health history and physical exam to assess pain characteristics including: location, intensity, quality, duration, and relieving and exacerbating factors. There was a campaign in the 1990s to make pain "the fifth vital sign" which increased visibility of pain assessments, but this heavy emphasis on addressing pain resulted in a number of unintended consequences including opioid abuse, addiction, and diversion. Although there has been growing hesitation with addressing pain in the clinical setting, by categorizing the type of chronic pain, the family physician can better determine patient treatment options.

A functional assessment is essential for patients in chronic pain [5]. Tools for use in clinic are numerous and include Numerical Rating Scales (NRS), Faces Pain Scale-Revised (FPS-R), and the Pain, Enjoyment, and General Activity questionnaire, along with the Physical Functional Ability Questionnaire by the Institute for Clinical Systems Improvement. In recent years there has been a gradual shift away from numerical assessment toward a focus on an evaluation of function and quality of life. Patients should be aware of these goals, and function should be tracked over time.

In addition to assessing the patient, family physicians must set expectations for pain management at the first visit. Chronic pain is a chronic disease and should be managed as such. Many patients will require multiple modalities, self-management skills, and more than one medication trial to achieve improvement in their daily function.

Types of Pain and Treatment Options

Pain is primarily classified as nociceptive or neuropathic. Nociceptive pain is caused by tissue injury and includes inflammatory, muscular, and mechanical pain. Neuropathic pain is caused by damage to or dysfunction of the central or peripheral nervous systems. Importantly, nociceptive

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and neuropathic pain systems are not mutually exclusive and patients can be affected by both types of pain. Classification of mechanism for a given patient can be helpful in guiding therapy [6].

Inflammatory pain – Arthritis, surgery, and infection are potential causes of inflammatory pain. Hallmarks of inflammatory pain on physical exam are edema, heat, erythema, and pain at the site of an injury. Treatment typically involves NSAIDs, corticosteroids, or immune-modulating agents to control the inflammation.

Muscular pain – Muscle soft tissue pain typically occurs after an injury and involves pain in one or more areas of muscle, loss of range of motion, as well as tenderness over the affected muscle groups. Myofascial pain is a common cause of chronic pain and is best managed by physical therapy and restoring muscle balance over providing medication [6]. Trigger point injections or acupuncture may be useful.

Mechanical pain – Mechanical pain is often caused by compression due to a cyst or tumor, fracture, degeneration, or dislocation. Pain is aggravated by activity and can be relieved by rest [6]. Most chronic neck pain and visceral pain fall into this category. Chronic low back pain can also be in this category but is often multifactorial. Treatment may be surgical in the case of cysts, fractures, and impingement.

Neuropathic pain – Common examples of neuropathic pain include diabetic neuropathy, postherpetic neuralgia, carpal tunnel, multiple sclerosis, and poststroke pain. Neuropathic pain is often described as "shooting" or "stabbing" but can also present as numbness, tingling, and increased sensitivity to benign touch (allodynia) [6]. Neuropathic pain is less responsive to opioid analgesics [7]. Treatment options for neuropathic pain are numerous, but can be generally divided into two categories: disease-specific treatments or symptom management. When discussing disease-specific treatments, the goal is to treat the underlying malady, such as improved glucose control for diabetic neuropathy or surgery for nerve decompression. First-line treatment options for symptom management include anticonvulsants, tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [6].

There is an additional classification for "other pain" that is currently evolving as we develop a better understanding of the mechanism. This has historically been known as "functional pain disorders" and includes fibromyalgia, irritable bowel syndrome, complex regional pain syndrome, and other conditions which may have started as nociceptive, but evolve to include sensitization disorders.

Non-opioid Pharmacologic Treatments for Pain

See Refs. [5, 6, 8] (Table 1)

Muscle Relaxants

Although commonly used for muscle spasms and to help alleviate acute pain, there is little evidence to support the use of muscle relaxants such as cyclobenzaprine (Flexeril) and tizanidine (Zanaflex) for chronic low back pain [6, 8]. These muscle relaxants are typically used in combination with an NSAID or acetaminophen. Carisoprodol (Soma) is structurally similar to alprazolam, has little utility in the management of chronic pain, and can be habit-forming [6]. If used chronically, muscle relaxants cause central relaxation and may carry the risk of physical dependence [8]. Baclofen is a commonly used antispasmodic agent which may improve neuropathic pain and may be less habit-forming than muscle relaxants [6, 8].

Role of Opioids in Chronic Pain

Current recommendations from the Center for Disease Control and Prevention (CDC) are to refrain from using opioids as the first line in pain therapy [9]. Although there are guidelines which have been developed to help clinicians safely and effectively treat chronic non-cancer pain (CNCP) with opioids, many of them are based on limited

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Table 1 Common Suggestions for Chronic Pain Medications and Dosages

Drug name	Usual dose	Maximum dose	Comments
Acetaminophen (Tylenol, others)	325–1,000 mg po q4–8 h respectively	3,000 mg/day	Recommended for noninflammatory osteoarthritis. May require maximum dose for 1 week for chronic pain trial. Avoid with chronic alcoholism. Monitor OTC medications for risk of accidental overdose
Nonsteroidal anti-inflammatory drugs (NSAIDs)			
Ibuprofen (Motrin, others)	200–800 mg po q4–6 h	3,200 mg/day	NSAIDs in recommended doses usually provide superior analgesia compared with aspirin, but do not produce the same analgesic effect in all patients. Major adverse effects are as follows: 1. Increased risk of serious cardiovascular thrombotic events, including myocardial infection and stroke. Elevated blood pressure may also be seen especially in the elderly and in conjunction with beta-blockers or angiotensin-converting enzyme inhibitors 2. Fluid retention in patients with congestive heart failure 3. Acute renal failure or renal insufficiency 4. Drowsiness and confusion 5. Reversible inhibition of platelet aggregation 6. Anaphylaxis in aspirin-sensitive patients 7. Peptic ulcer disease, regardless of mode of administration, especially in the first month of therapy Adding a proton pump inhibitor, H2-receptor antagonist, or misoprostol may decrease GI toxicity Use with caution and for the shortest time possible in the elderly
Naproxen (Naprosyn)	500 mg po q12h	1,000 mg/day	
Indomethacin (Indocin)	25–50 mg po q8h	200 mg/day	
Ketorolac (Toradol, others) For Pts <65 y/o	20 mg po, then 10 mg q4–6 h (start at 10 mg po if <50 kg)	40 mg/day	
	60 mg IM as a single dose	120 mg/day	
Diclofenac (Cataflam, Cambia)	50 mg po q8h or q12h for SR	200 mg/day	
Meloxicam (Mobic)	5–15 mg daily	15 mg/day	May be more selective for COX-2 at low dose (7.5 mg)
Nabumetone (Relafen)	1,000 mg as a single dose	2,000 mg/day	
Celecoxib (Celebrex)	200 mg po q12h	400 mg/day	Selective COX-2 inhibitors and NSAIDs have demonstrated decreased gastrointestinal complications compared with nonselective NSAIDs. They do not inhibit platelet aggregation Less effective than full doses of ibuprofen or naproxen
Tricyclic antidepressants			Primarily used for neuropathic pain. Analgesia achieved at lower dose (20–100 mg/day) than antidepressant dose (150–300 mg/day). Contraindications include heart failure, ischemic heart disease, and arrhythmias. Side effects include confusion, urinary retention, orthostatic hypotension, dry mouth, drowsiness, and nightmares Use cautiously in patients at risk for suicide or accidental overdose due to potential for lethal cardiotoxicity Nortriptyline and desipramine are better tolerated than amitriptyline and imipramine Gradually taper dosing
Nortriptyline (Pamelor)	10–100 mg qHS	150 mg/day	
Desipramine (Norpramin)	25–150 mg daily	150 mg/day	
SNRI			Better for neuropathic and "other" pain. Taper over 2 weeks to discontinue. Better tolerated than TCA Common SE of HA and nausea
Venlafaxine (Effexor)	75–150 mg po daily	225 mg	
Milnacipran (Savella)	Tapered up to 50 mg po BID	200 mg/day	
Duloxetine (Cymbalta)	Tapered up to 60 mg daily	60 mg/day	Specifically used for diabetic neuropathy, fibromyalgia, OA of the knee, chronic low back pain, and nonradicular neck pain. No known cardiovascular risk. Nausea is a common side effect

(continued)

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Table 1 (continued)

Drug name	Usual dose	Maximum dose	Comments
Anticonvulsants (calcium channel alpha-2-delta ligands)			Typically used for neuropathic pain and chronic headaches. Can be added to TCA. Similar efficacy to TCA
Gabapentin (Neurontin)	Titrate up to 300–1,200 mg TID	3,600 mg/day	Start at 100–300 mg qHS, and titrate to effective dose. Common side effects include fatigue, impaired concentration, and peripheral edema. May increase risk of suicidal ideation. Reduce dose in renal impairment
Pregabalin (Lyrica)	75–300 mg po BID	450–600 mg/day	FDA approved for fibromyalgia and neuropathic pain. May have anxiolytic benefits
Carbamazepine (Tegretol)	200–400 mg daily	1,200 mg/day	Important to test for HLA-B*1502 allele in patients at increased risk. Also risk of agranulocytosis and aplastic anemia. Effective for trigeminal, glossopharyngeal, or postherpetic neuralgia, and diabetic neuropathy
Oxcarbazepine (Trileptal)	300–900 mg po BID	1,800 mg/day	Off-label use, but may have fewer side effects than carbamazepine
Topical agent			
Lidocaine patch (Lidoderm)	1–3 patches for 12 h per day	3 patches/day	Approved for postherpetic neuralgia. Minimal evidence to support other uses
Diclofenac (Voltaren gel)	2–4 g topical q6–8 h	32 g/day	Topical NSAID with low risk of systemic side effects

All medications and dosages are for adults over 18 y/o, and dosage should be re-evaluated if patient has renal or hepatic dysfunction or variance in pharmacodynamics
OTC over the counter, *COX* cyclooxygenase, *NSAID* nonsteroidal anti-inflammatory drug, *SR* sustained-release, *TCA* tricyclic antidepressant, *SNRI* serotonin-norepinephrine reuptake inhibitor

data [10, 11]. Most trials involving CNCP are short (<3 months) and evaluate pain scores and not patient function, and there is mounting evidence that the potential risks of long-term opioid use outweigh additional benefit when non-opioid options are available [12]. This chapter is focused on CNCP, but even the American Society of Clinical Oncology (ASCO) advocates for the use of systemic non-opioid analgesics to relieve chronic pain and judicious use of opioids in patients who are not responding to conservative pain management approaches, along with precautions to minimize opioid abuse and addiction in these patients. General consensus for CNCP continues to be avoidance of opioids if possible, with preferential use of non-pharmacologic and non-opioid pharmacologic therapies [13].

If opioids are to be used for CNCP, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapies as appropriate. The clinician should also establish treatment goals with all patients before starting opioid therapy, including realistic goals for pain and function, and consideration of how therapy will be discontinued if benefits do not outweigh risks [9].

Mitigating Opioid Risks

When selecting opioids, current guidelines are to prescribe immediate-release opioids instead of extended-release/long-acting opioids, prescribing at the lowest possible effective dose, and regular reassessment of patient benefits and risks. Particularly high-risk populations include patients with kidney disease, those that are 65 years of age or older, pregnant patients, those with mental health conditions, those with substance use disorder, and patients with prior nonfatal overdose. Typically, risk is mitigated with strategies like offering naloxone to those at increased risk and using validated screening tools, such as the Drug Abuse Screening Test (DAST), Alcohol Use Disorders Identification Test (AUDIT) the single question screener, the Opioid Risk Tool, Addiction

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Behaviors Checklist, and the Screener and Opioid Assessment for Patients with Pain in order to screen patients for substance use or misuse [5].

Treatment agreement example includes the following:

- Risks of opioid use, including psychological and/or physical dependence, addiction, and overdose.
- Agreement to keep all schedule appointments
- Alternative treatments and adjunct therapies
- Agreement to not use illicit drugs
- Agreement to not divert medication (sell or share medications)
- Agreement to not attempt to obtain controlled medication from any other provider
- Agreement that refills will be made only during regular business hours, typically at the same pharmacy
- Agreement to regular blood or urine tests
- Agreement to only use medication as prescribed

Documenting informed consent and expectations is crucial and can be accomplished using treatment agreements or "pain contracts" between the prescribing physician and the patient. There is some evidence that treatment agreements may improve patient compliance [12]. Using these agreements, providers can also discuss expectations of random urine drug testing (for both assessment of therapeutic adherence and evidence of nonuse of illicit drugs), pill counts, and replacement of lost/stolen prescriptions and counsel to avoid excessive amounts of alcohol. During the discussion of the treatment agreement, physicians should establish reasonable expectations at the start of an opioid trial (see list below). Total pain relief with opioids is not realistic. The average benefit on a 10 point pain scale is 2–3 points [11]. A successful opioid trial typically results in a 30% reduction in pain or a 30% improvement in function [12].

Legislation for prescription drug monitoring programs (PDMP) has been authorized in 49 states, DC and Guam, which has reduced doctor shopping, diversion, and prescription drug abuse [13].

Every patient on chronic opioid therapy should have periodic urine drug screening (UDS) [12]. The frequency of testing can be based on the patient's overall risk of misuse. Although utilizing these screens is important, the interpretation of results is not always straightforward and must be considered in the context of patient behavior and overall compliance [11]. Unexpected positive results should be confirmed by more specific means, and a discussion with the laboratory may be helpful to determine concentrations necessary for a positive result when the prescribed opioid is not present (see list below) [9].

Evidence also discourages clinicians from prescribing opioid pain medications and benzodiazepines concurrently whenever possible. Concurrent use likely puts patient at greater risk of central nervous system (CNS) depression and can decrease respiratory drive. Similar effects may be found if other CNS depressants are used (muscle relaxants, hypnotics).

High-risk patients and those with significant psychiatric comorbidities, cognitive impairment, or history of drug abuse should be managed only by providers experienced with this population, and comanagement with psychiatry or an addiction specialist is strongly recommended [11].

2016 CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care [9]

- **Determining when to initiate or continue opioids for chronic pain**
  - Opioids are not first-line or routine therapy for chronic pain.
  - Establish and measure goals for pain and function.
  - Discuss benefits and risks and availability of non-opioid therapies with patient.
- **Opioid selection, dosage, duration, follow-up, and discontinuation**
  - Use immediate-release opioids when starting.
  - Start low and go slow.

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  - When opioids are needed for acute pain, prescribe no more than needed.
  - Do not prescribe ER/LA opioids for acute pain.
  - Follow-up and re-evaluate risk of harm; reduce dose or taper and discontinue if needed.
- **Assessing risk and addressing harms of opioid use**
  - Evaluate risk factors for opioid-related harms.
  - Check prescription drug monitoring program for high dosages and prescriptions from other providers.
  - Use urine drug testing to identify prescribed substances and undisclosed use.
  - Avoid concurrent benzodiazepine and opioid prescribing.
  - Arrange treatment for opioid use disorder if needed.

Discontinuation of Opioids

Current recommendations are to reduce and eliminate opioid therapy whenever possible. If patients have baseline improvement or are not progressing toward established treatment goals, show repeated aberrant behaviors, or are suffering intolerable adverse effects, discontinuation of opioid therapy is encouraged [11]. A conservative opioid taper, with weekly decreases of 5–10% of the original dose, is usually well tolerated, although more aggressive decreases are possible [12]. Patients are encouraged to receive appropriate psychosocial support if needed during the taper regimen. While not usually life-threatening, opioid withdrawal can be unpleasant. Autonomic symptoms (sweating, tachycardia, myoclonis) can be managed with clonidine 0.1–0.2 mg orally every 6–8 h, with baclofen or tizanidine available as alternatives. Anxiety, lacrimation, and dysphoria may be managed with hydroxyzine (25–50 mg TID PRN) or diphenhydramine (25 mg q6h PRN). Myalgia is often managed with NSAIDs or acetaminophen [14]. For patients who are abusing the medication or noncompliant with the taper schedule, referral for inpatient detoxification is encouraged [12].

All patients with aberrant behavior should be offered addiction resources [11]. Office-based treatment with buprenorphine/naloxone may be appropriate for patients with opioid dependence. This treatment is an alternative to methadone maintenance and can be offered by primary care providers after obtaining further education and a special licensure from the DEA. More information can be found at http://buprenorphine.samhsa.gov.

Other Interventions for Pain Management

Although outside the scope of a traditional primary care setting, it is important to understand the other available options for our patient population who have not improved with typical multidisciplinary outpatient therapies.

Injections – Typically a local anesthetic is used, often mixed with a steroid, and injected either directly into trigger points, the epidural, or used to temporarily dull the nerves providing sensation to the area.

Ablation – Usually performed either chemically (using local anesthetic) or using electrical current (radiofrequency ablation) for denervation, which may provide pain relief for 6–12 months.

Implantables – Intrathecal pumps allow continuous doses of a drug to be injected directly into the dura mater covering the spinal cord, which allows small doses of the drug to be released, blocking downstream innervation and acting as a neuromodulator. Another form of neuromodulation is spinal cord stimulation, which places electrodes in the epidural space to stimulate specific pathways in the spinal cord with electoral impulses using a remote control when the patient feels pain. Although the exact mechanism isn't fully understood, it seems to target multiple muscle groups directly from the spine and alter afferent innervation.

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Non-pharmacologic Modalities

Treatment plans for chronic non-cancer pain must include more than just medications, and the benefits may extend to more than just the pain management. The Department of Defense, the Department of Veterans Affairs (VA), and the National Institute on Drug Abuse have been working together to create pain protocols and have found that service members who receive nondrug therapy for chronic pain had a significantly lower risk of alcohol or drug use disorder, accidental poisoning, suicidal ideation, and self-inflicted injuries. Research suggests that patients who start with physical therapy or manipulation as a first-line treatment for lower back pain are less likely to proceed to short- or long-term opioid use [15].

Exercise therapy is recommended for chronic low back pain, knee pain, as well as other types of chronic pain and can reduce functional limitations [6]. Patients with CNCP are often deconditioned due to inactivity, and providers should recommend gradually increasing general activity levels as well as formal exercise. Often an exercise physiologist can help determine appropriate exercise regimens to help recover from specific injuries or pain syndromes and can be designed to help patients break the cycle of inactivity, deconditioning, muscle dysfunction, and pain. Our current understanding of the process is that dynamic movement helps nutrient replacement in the cartilage given generally poor blood supply. It can also help strengthen collateral muscles, reducing impact on joints, and some theories point to exercise helping engage endogenous opioid systems [16].

In addition, manual therapy, like massage and musculoskeletal manipulation, has been shown to reduce chronic pain due to low back pain, knee osteoarthritis, and fibromyalgia [6]. Often, manual therapy can help with short-term pain relief, and this increased exercise and ability to participate in physical therapy can help with long-term healing.

Transcutaneous electrical nerve stimulation (TENS) therapy uses low-voltage electrical current through electrodes placed on the surface of the skin to provide pain relief. There are multiple theories on how it works, from neuromodulation and blocking transmission of pain signals, to stimulating the nerves and raising endorphins with modified pain perception [17].

Acupuncture has been used for medical treatments for millennia and has found a resurgence with the incorporation of "medical acupuncture" and physicians and other western clinicians bringing it into daily practice. Treatment typically consists of inserting fine needles into the body in patterns designed to influence the "flow of qi" in one of the subdivisions of the energy circulation networks according to the practice of traditional Chinese medicine [18]. Western theories include creating microperforations in the muscle fascia and increasing inflammation and irritation in effected trigger points, improving blood flow, and thus improving the healing process. Typically treatments are spaced out more and more, with home cares done in the interim to continue long-term treatment. It is most useful as a primary therapy for musculoskeletal pain (acute and chronic) and can be added as a complement to other treatments [19].

Psychotherapy is being utilized more frequently as a treatment modality for patients with CNCP. Psychotherapy focuses on improving the patient's quality of life, social functioning, and mood rather than decreasing the level of pain [20]. Cognitive-behavioral therapy (CBT) and mindfulness-based stress reduction are two psychological interventions that therapists can use to teach patients how to manage their pain and engage in a full life despite their pain. Unfortunately many patients struggle with the cost of these services, but mindfulness and diaphragmatic breathing are methods that can also be taught in primary care settings. Providers can also utilize modified CBT techniques when working with patients (see list below).

Brief incorporation of CBT in clinical practice

- Encourage your patient to take an active role in their pain management.
- Tell your patient that you believe the pain is real and you will work together to manage it.

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- Do not let pain dictate activity or appointments. Schedule regular visits and medications at regular intervals instead of as needed.

Quality of Life and the Chronic Disease Model

Chronic non-cancer pain is complex and following current treatment guidelines requires significant clinical resources. However, this is not unlike other chronic illnesses. Using a chronic care model within primary care has clearly improved the care of patients with chronic illnesses such as diabetes, congestive heart failure, and asthma [21]. Chronic non-cancer pain must be approached in the same manner. A comprehensive approach that includes risk assessment, treatment agreement, patient self-management, and care coordination can improve adherence to guidelines, pain disability, and pain intensity [22].

Sleep – Sleep disturbance is common with chronic pain, and many feel that the two exacerbate one another in the pain cycle (see Fig. 1). Some turn to hypnotics to help alleviate the issues, but typically starting with appropriate sleep hygiene and cognitive behavioral therapy and properly managing the underlying cause of the pain tend to break the cycle.

Pain diary – Keeping a pain diary may be a very useful exercise, in that it may reveal patterns in pain intensity as well as things that may make it better or worse. It can also help convey associated symptoms and quality of the pain (burning, shooting, aching, etc.), which may help with diagnosis and management in the clinical setting.

Goal setting – Setting daily targets that are achievable may help with the progression of activity and management for our chronic pain patients.

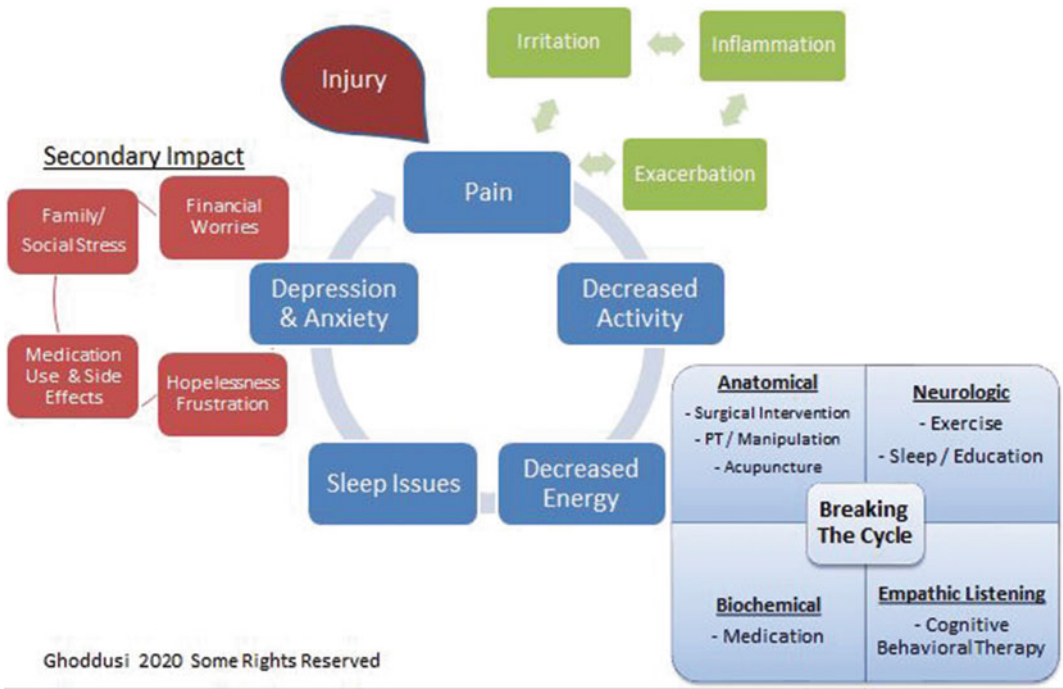


Fig. 1 Pain cycle

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Care of the Dying Patient

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Franklin J. Berkey and Nicki Vithalani

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General Principles

Definition/Background

In contrast to the numerous maladies described elsewhere in this textbook, successful care of the dying patient is not measured in terms of convalescence but rather in achievement of a "good

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death." While the circumstances of death among the seriously ill in US hospitals are well defined – a high prevalence of pain and frequency of invasive procedures – the characteristics of a "good death" vary between patient, family, and provider [1, 2]. Frequently cited characteristics of a "good death" include control of severe pain, reduction of stress and anxiety, provider compassion, and the perceived knowledge and expertise of the physician [3]. However, patients with terminal conditions often report a sense of abandonment by their primary provider [4]. Increased end-of-life education among family physicians is critical in shifting patient deaths out of the hospital and into the comforts of home in effort to improve end-of-life care [5].

Palliative Care and Hospice

Palliative care is the field of medicine focused on improving quality of life for patients and families facing serious illness. Appropriate at any stage of illness, palliative care is often provided concurrent with curative treatment. In 2019, 72% of hospitals in the United States with at least 50 beds staffed a palliative care team, a marked increase from 2000 when only 7% reported the same [6].

Hospice is an insurance benefit that incorporates palliative care to provide a coordinated team approach for patients with a prognosis of six months or less. Hospice utilization is increasing. Compared to 2000, Medicare decedents in 2015 were more likely to be on hospice (21.6% to 50.4%) and less likely to die in an acute care facility (32.6% to 19.8%) [7]. While cancer a diagnosis previously accounted for the majority of the hospice referrals, current data reflects a broad array of terminal diagnoses. In 2017, 70% of hospice admissions were for noncancer diagnosis, with heart disease (17.6%) and dementia (15.6%) leading the list of noncancer admissions [8].

Centers for Medicare and Medicaid Services (CMS) certified hospice programs must provide core services including a physician medical director, hospice nurse, social worker, and counselors for bereavement, dietary, and spiritual needs. Additional services include physical therapy, occupational therapy, speech pathology, home aide services, and volunteer services. All recommendations from the interdisciplinary team are forwarded to the patient's primary physician, as the hospice concept aims to support the patient's personal physician as the primary provider.

Hospice eligibility guidelines vary by diagnosis, but all require a prognosis of 6 months or less as certified by two physicians. Hospice patients are certified for two initial 90-day periods, after which recertification must take place every 60 days. Recertification periods are unlimited, as long as the patient's prognosis, judged by their terminal diagnosis and progression of symptoms, continues to be 6 months or less from the date of recertification.

Surprising to many, hospice patients often live longer than similar patients not enrolled in hospice. One study found that hospice patients with CHF lived an average 81 days longer than disease-matched patients not in hospice, and similar results were noted with lung (39 days), colon (33 days), and pancreatic cancer (21 days) [9]. Researchers theorize the difference in life span is due to a combination of factors, including avoidance of side effects related to aggressive treatments, the increased monitoring and symptom management provided in hospice, and the interdisciplinary focus on the patient's emotional needs and well-being.

End-of-Life Patient Communication

Effective communication is the initial step in providing end-of-life care. However, physicians often avoid end-of-life conversations for fear of causing depression, taking away hope, and shortening life span with hospice involvement [10]. To the contrary, end-of-life discussions are associated with less aggressive medical care, earlier hospice referral, improved quality of life, and better bereavement adjustment [11].

The SPIKES Protocol provides a six-step plan to deliver bad news to a patient [12]. The protocol guides the provider in the four critical objectives

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in delivering bad news: gathering information from the patient and assessing understanding, delivering the medical information, providing support, and developing a follow-up plan.

- (**S**) **Setting**: Provide a quiet place for the discussion, minimize interruptions, and involve significant others. Sit, do not stand.
- (**P**) **Perception**: Determine what the patient already knows, and his/her perception of their illness. "*When you first felt the lump in your breast, how serious did you think it was*?"
- (**I**) **Invitation**: Determine how much the patient would like to know and seek permission to provide the new information. "*Is it OK if I share the results of the biopsy with you now*?"
- (**K**) **Knowledge**: Share the bad news, providing information in small amounts, using plain language and checking frequently for understanding. Preface the news with a warning. "*Unfortunately, I have some bad news to tell you today.*"
- (**E**) **Empathy**: Acknowledge and address emotions as they arise; provide empathy. "*I see this news comes as quite a shock to you*."
- (**S**) **Strategy**: Address questions, determine next step, and plan follow-up. "*I will see you again in five days, but please call if you have questions*."

Prognosis at End of Life

Physicians tend to be overly optimistic when estimating survival [13]. Physician optimism, combined with patient self-deception, is an explanation for why in a survey of nearly 1200 patients with metastatic colorectal and lung cancer, 81% and 69% of the patients, respectively, believed their therapy was likely to provide a "cure" [14]. Contrary to popular belief, an accurate prognosis does not eliminate a patient's hope but rather may help a patient make better informed decisions that allow for an improved quality of life.

While determining survival time is difficult, there are tools to aid the family physician. For malignancies, established survival statistics for each stage of a cancer provide a starting point. The Palliative Performance Scale (PPS) (Table 1),

Table 1 Palliative performance scale

	Ambulation	Activity & disease evidence	Self-care	Intake	Level of consciousness
100	Full	Normal, no disease	Full	Normal	Full
90	Full	Normal, some disease	Full	Normal	Full
80	Full	Normal with effort, Some disease	Full	Normal or reduced	Full
70	Reduced	Unable to do normal work, some disease	Full	Normal or reduced	Full
60	Reduced	Cannot do hobbies/housework, sig. disease	Occasional assistance	Normal or reduced	Full or confusion
50	Mainly sit/lie	Cannot do any work, extensive disease	Considerable assistance	Normal or reduced	Full or confusion
40	Mainly in bed	Cannot do any work, extensive disease	Mainly assistance	Normal or reduced	Full or drowsy or confusion
30	Bed Bound	Cannot do any work, extensive disease	Total care	Reduced	Full or drowsy or confusion
20	Bed Bound	Cannot do any work, extensive disease	Total care	Minimal	Full or drowsy or confusion
10	Bed Bound	Cannot do any work, extensive disease	Total care	Mouth care	Drowsy or coma
0	Death	–	–	–	–

Source: [15]

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a validated scale assessing overall functioning of a terminally ill patient, can assist the physician in refining the prognosis and determining hospice eligibility [16]. While incurable malignancies tend to follow a predictable course, diseases related to end-stage organ failure follow a more erratic and less predictable course.

The Functional Assessment Staging Scale (FAST) is a tool to stage dementia and determine hospice eligibility (Table 2). While patients with mild to moderate dementia often require substantial care, hospice-appropriate dementia patients have a FAST score of at least 7C and one or more of the following comorbid predictors: aspiration pneumonia, pyelonephritis, septicemia, multiple stage three to four decubiti, and fever despite antibiotics. Similar to end-stage organ disease, there is great variability among dementia patients, and the aforementioned criteria have limitations in predicting a 6-month prognosis. Providers may use Local Coverage Determination (LCD) guidelines, provided by the Centers for Medicare and Medicaid Services (CMS), in determining hospice appropriateness for all diagnoses.

Table 2 Functional assessment staging (FAST)

Score	Characteristics
1	No difficulties
2	Subjective forgetfulness
3	Decreased job functioning and organizational capacity
4	Difficulty with complex task (personal finances, planning dinner)
5	Requires assistance with activities of daily living (ADLs)
6	(**A**) Unable to dress without help (**B**) Unable to bathe properly (**C**) Inability to self-toilet (**D**) Urinary incontinence (**E**) Fecal incontinence
7	(**A**) Speaks ≤6 intelligible different words in the course of an average day (**B**) Speech limited to the use of a single intelligible word (**C**) Cannot ambulate (**D**) Cannot sit up without assistance (**E**) Cannot smile (**F**) Cannot hold up head independently

Source: [17]

Note: A patient must fulfill criteria in successive order. For example, a patient who is incontinent of bowel and bladder, cannot ambulate (due to a recent hip fracture), and speaks 20 words is scored 6E (not 7C)

End-of-Life Pain Management

Dr. Cicely Saunders, founder of the modern hospice movement, developed the concept of total pain to describe the suffering experienced by patients and their family. The four major components of total pain – physical pain, social pain, psychological pain, and spiritual pain – are interrelated, and often the sum is greater than the individual components. Successful end-of-life pain management is dependent on attention to all four components, with recruitment of social workers, spiritual leaders, and other allied professions often needed.

Physical Pain

The World Health Organization cancer pain ladder provides a starting point for the treatment of end-of-life pain. The ladder employs a three-step approach, starting with nonopioids such as acetaminophen and ibuprofen (step 1), progressing to weak opioids such as codeine (step 2), and finally strong opioids such as morphine (step 3). However, effective management of end-of-life pain will frequently require a starting point other than step 1 and accelerated progression through the steps. While acetaminophen is an appropriate first step for mild to moderate pain, its use as an adjunct to higher doses of opioids is limited [18]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also useful as an initial step, and particularly useful as an adjunct to opioids in patients with metastatic bone lesions [19].

Effective pain control with opioid medications is best achieved with a combination of scheduled long-acting opioids in combination with short-acting "rescue" doses. For opioid-naïve patients, the starting dose is usually 5–10 mg of morphine equivalents every 4 h. Unlike pain management in the nonterminal patient, end-of-life pain management often requires quick titration. A patient's use of short-acting pain medication is calculated over

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the first 24 h, and then converted to a long-acting form. Thereafter, breakthrough dosing should start at 10–15% of the new scheduled daily long-acting dose of the same opioid, usually provided every 2–4 h. As a general rule, the need for four or more "rescue" doses in a 24-h period warrants an increase in the long-acting dose. Also, "rescue" doses should be given prior to potentially pain-provoking procedures and daily activities (wound care, dressing change, bed repositioning, bathing).

Methadone, due to its low cost, high bioavailability, and effectiveness at treating neuropathic pain, is frequently used in end-of-life care. It is also useful in patients with renal impairment, as 60% of its elimination is nonrenal (primarily fecal). Titration is difficult, drug interactions are numerous, and consultation with a palliative care provider is recommended.

While uncommon in hospice and palliative care, opioid toxicity presents as increased drowsiness, confusion, and hallucinations. The side effects often reverse with holding subsequent doses. If naloxone (Narcan) is required, a modified dose for end-of-life patients avoids an abrupt pain "rebound." In this circumstance, a dilute solution obtained by mixing 0.4 mg naloxone in 10 ml of normal saline is delivered by slow IV push 1 ml every 4–5 min until the side effect resolves. Myoclonus, a rare side effect that can be seen at any dose of opioid, is best handled with opioid rotation. In opioid rotation, a morphine-equivalent dose is calculated, reduced by 20–30% to account for incomplete cross-tolerance, and then started in place of the original opioid. Consultation with a palliative care pharmacist is often required.

Neuropathic Pain

There are several adjunctive therapies for treating neuropathic pain. Duloxetine (Cymbalta), in a randomized, double-blind, placebo-controlled study, demonstrated significant improvement in neuropathic pain related to chemotherapy [20]. Tramadol (Ultram), due to its action on serotonin and norepinephrine, provides relief of neuropathic pain, as well as improvement in sleep and performance status [21]. Both Duloxetine and Tramadol interact with serotonin enhancing medications, and Duloxetine can decrease the efficacy of tamoxifen. Tricyclic antidepressants (TCAs) are effective in treating neuropathic pain [22]. Dosed at bedtime, TCAs are also useful as a sleep aide. Most evidence supporting TCAs is in noncancer patients, and full response may take up to 1 month. Gabapentin (Neurontin), titrated over 3–5 days, is also an effective adjunct to opioid therapy for neuropathic pain [23]. Ultimately, a combination of medications may be needed, with titration of each medication dependent on side effects.

Bone Pain

Metastatic bone pain is common in end-of-life care, particularly in patients with breast and prostate cancer. NSAIDs are effective alone and in combination with opioids in treating pain due to skeletal metastasis. Dexamethasone (Decadron) has been shown to reduce pain associated with bony metastasis and may be favorable compared to other steroids due to less fluid retention. Steroids are also effective in treating anorexia, weakness, headache, and nausea and vomiting, with an improvement of symptom intensity seen in less than 3 days on average [24]. Bisphosphonates may be useful in patients with widespread bone pain, especially in patients with multiple myeloma and concomitant hypercalcemia [25]. Radiation therapy is a useful palliative intervention for cancer-related bone pain and appropriate for hospice patients.

Grief and Depression

Grief and depression are common among patients and families dealing with a terminal illness. Grief, while it may cause suffering, is considered both adaptive and healthy. Depression is maladaptive and can significantly increase suffering and reports of pain, decrease quality of life, and shorten survival [26]. Depression is highly associated with brain, breast, lung, pancreatic, and

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oropharyngeal malignancies and less associated with colon and gynecologic tumors [27, 28]. Treatment with both SSRIs and TCAs is effective in depressed patients with terminal illness, although life expectancy may limit usefulness. Both medication classes may also have secondary beneficial effects based on side effects (tricyclic for neuropathic pain and insomnia, for example). Mirtazapine (Remeron), used at night, is also helpful in the treatment of insomnia and anorexia. In patients with prognosis of less than 4–6 weeks, psychostimulants may reduce depressive symptoms within days of commencement [29].

Nausea and Vomiting

Nausea and vomiting are common complaints in the dying patient, especially in those with advanced cancer. Frequently seen as a side effect of chemotherapy, nausea, and vomiting are also a result of anxiety, obstruction, and inflammation. In addition to traditional antiemetic agents, benzodiazepines are useful in treating nausea related to anxiety, and haloperidol (Haldol) is helpful in refractory symptoms near the end of life.

Bowel obstruction is frequently associated with ovarian and colon cancers. Nonsurgical treatments include cessation of oral intake, nasal-gastric decompression, octreotide (Sandostatin), and corticosteroids. Octreotide, which is administered either intravenously or subcutaneously, inhibits the accumulation of intestinal fluid. Dexamethasone, in daily doses between 6 and 16 mg intravenously, has been shown to relieve symptoms associated with bowel obstruction.

Constipation

Constipation is a frequent pain-provoking symptom in end-of-life care. Decreased mobility, dehydration, and opioid medications are all risk factors for constipation. A stool regimen should be implemented as soon as the symptom arises, or with introduction of an opioid medication, whichever comes first. Hospice programs usually institute an algorithm which includes a daily combination of both osmotic and stimulant laxatives which are increased each day that the patient is without a bowel movement. For example, sennoside (Senna) is given 2–4 tabs nightly along with polyethylene glycol (Miralax) daily. If a patient does not have a bowel movement on the second day, the sennoside is increased by two tablets (in divided doses), and the polyethylene glycol is increased to twice daily. If a patient is without a bowel movement on day three, a rectal exam is usually indicated, with subsequent use of enemas and further titration of the laxatives. Higher-than-usual laxative doses are often required in palliative care. There is no evidence to support docusate (Colace) as softening agent in end-of-life care. For intractable opioid-induced constipation, opioid receptor antagonists such as methylnatrexone (Relistor) and naloxegol (Movantik) are effective [30].

Dyspnea

Primary management of the dying patient with moderate to severe dyspnea is achieved with opioids. Etiologies are multiple, including bronchospasm, effusions, thick secretions, and anxiety. In addition to disease-specific treatments, opioids are effective for patients with COPD, CHF, and terminal cancer [31]. Immediate-release morphine, 2.5 mg to 5 mg every 4 hours, is a reasonable starting point in the opioid-naïve patient. Titration, including the use of long-acting opioids, is similar to that for physical pain. Benzodiazepines are a useful adjunct to opioid therapy in relieving dyspnea attributed to anxiety. While evidence supporting the use of supplemental oxygen in nonhypoxic patients reporting dyspnea is anecdotal, oxygen is often trialed in the hospice patient as the usual Medicare qualification guidelines do not apply. Small studies have also demonstrated a symptomatic benefit with the gentle breeze of a low-set fan.

Recommendation for the Final Hours

Signs of active dying include irregular respirations, accumulation of oral secretions, decreased urine output, and fever unresponsive to antipyretics. It is generally accepted that dying patients

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may have a greater awareness than ability to respond, and family is encouraged to talk to the dying. To minimize sacral pressure, the head should be lowered to less than 30° and the patient turned every 60–90 min. Wound care goals are shifted from healing to comfort, and dressing changes are minimized. The use of dark or red-colored sheets may reduce anxiety among bedside visitors when hemorrhage is a concern. Oral care, using an artificial saliva solution, is provided for comfort. A simple home remedy is made of 5 ml salt and 5 ml of baking soda mixed in 1 l of tepid water [32].

Excessive oral secretions ("death rattle") are treated with oral administration of 1% atropine eye drops (one to two drops SL every 4 h) or glycopyrrolate (1 mg SL or 0.2–0.4 mg SC/IV every 4 h). Hyoscyamine (Levsin) and scopolamine are also used.

Terminal delirium is defined as an irreversible agitation in the final hours of life. Highly stressful for caregivers and family, it is best managed with benzodiazepines. Lorazepam (Ativan) 1–2 mg elixir is given sublingually every hour as needed. Benzodiazepines, in addition to their anxiolytic effects, also serve as muscle relaxants to decrease contractures and provide prophylaxis for seizure activity, both unsettling symptoms for caregivers and family.

Advanced Directives: Living Wills/ Health Care Proxy/POLST

An essential part of end-of-life care involves advanced care planning. Family physicians, given their familiarity with the patient and family, are optimally positioned to assist with such planning.

Traditionally, advanced directives consisted of living wills, or documents which state a patient's wishes should they develop an irreversible condition that prevents them from making a decision. However, living wills do not translate into actionable medical orders and oftentimes are not readily available and are too vague to interpret. A health care proxy is someone who is familiar with and can make decisions in accordance with a patient's values and beliefs. However, in the event of an emergency, the proxy may not be available to consult, and Emergency Medical Services (EMS) providers cannot always follow the direction of a health care proxy.

In response to the shortcomings noted above, the Physician Orders for Life-Sustaining Treatment (POLST) provides patient wishes that translate into actionable medical orders. Started by a team at the University of Oregon in the late 1990s, POLST forms are currently operational in all 50 US states, although the name may vary [33]. While traditional advanced directives are designed for all adults and direct future care, POLST orders are for the seriously ill (life expectancy less than 1 year) and reflect current care. Through an informed and shared decision-making process, a health care professional completes the POLST orders (unlike a traditional advanced directive, which is completed by the patient). A POLST document provides orders regarding resuscitation in the event of pulselessness and apnea as well as decisions regarding level of intervention in terms of transport to the hospital, intubation, mechanical ventilation, noninvasive airway support (CPAP/BiPAP), antibiotics, and artificial feeding [34]. In states where POLST or similar programs are implemented, these orders are transferable between facilities as well as being usable in the prehospital setting (EMS).

Palliative Sedation, Physician-Assisted Suicide, and Euthanasia

There are no greater ethical issues in end-of-life care than palliative sedation, physician-assisted suicide, and euthanasia. While the details of these practices are beyond the scope of this chapter, family physicians need a basic understanding of the terms, if only to dispel myths and distinguish these extreme measures from more common and widely accepted symptom-relief modalities.

While the terms are often erroneously interchanged, there is a clear distinction in intent and practice of the three concepts. Palliative sedation is a last resort practice for the very small minority of patients in which traditional palliative measures cannot relieve intolerable suffering. By way of a reduction in consciousness, symptom

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relief is achieved. In palliative sedation, the intent is symptom relief, which distinguishes it from physician-assisted suicide, in which the intent is to hasten death. This delineation is strengthened by medical studies which demonstrate that palliative sedation does not hasten death [35]. Physician-assisted suicide, legal in only a few states, is distinguished from euthanasia in that the physician provides the medications for the patient to take by themselves. In euthanasia, which is illegal in the USA, the physician administers the medications to achieve death.

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Care of the Refugee

65

Michael Greene and Seif L. Nasir

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Definition

The 1951 Refugee Convention defines a refugee as someone who, "owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality, and is unable to, or owing to

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such fear, is unwilling to avail himself of the protection of that country" [1].

The United Nations High Commissioner for Refugees (UNHCR) estimates that there are over 70 million forcibly displaced people worldwide; of these, over 25 million are classified as refugees [2]. Understanding the definition of "refugee" as a person who was *pushed* out of their homeland by the fear of violence or persecution rather than *pulled* out of their homeland by economic or educational opportunities is an important aspect of navigating the needs and experiences of refugees as patients [3]. Worldwide, the people who make up refugees tend to be people who have higher skills, education, and occupational positions in their country of origin. Refugees also tend to be younger in age. The family physician should be aware that most refugees are not from poor or destitute backgrounds, but are often functional, independent, prominent, and highly successful individuals and families fleeing danger in their home country.

A second model for understanding the refugee experience highlights the stages of seeking refuge in which the affected may experience challenges that can manifest as social or medical problems that should be taken into consideration by a family physician (see section "Keller Stages of Refugee Experience" [4]). The perception of danger and making the decision to flee can be preceded by the loss of resources and/or forced unemployment. The process of escaping danger is often extremely dangerous and can expose refugees to physical and psychological traumas and the lack of food, water, and shelter. Even after arrival at their destination, refugees are often placed into camps or temporary housing of low quality and with inadequate resources. These situations often force refugees, even the most highly educated ones, into jobs of low-wage labor. Finally, the long-term consequences of flight and of assimilation to a new culture on mental health and psychological well-being are another challenge that refugees face. In addition to these interpersonal stressors, physicians should bear in mind the ways in which the residual effects of the refugee experience can include more practical barriers to providing care such as income and care-seeking behavior.

Keller Stages of Refugee Experience

- Perception of a threat
- Decision to flee
- Period of extreme danger and flight
- Reaching safety
- Camps and camp behavior
- Repatriation
- Settlement or resettlement
- Adjustment and acculturation
- Residual stages and changes in behavior caused by the experience

Despite large numbers of refugees around the world, very few well-established schema exist for dealing with the social, economic, and healthcare needs of refugees [5]. The lack of these programs is partially due to the mistaken belief that all refugee emergencies are unique problems. While there are certainly important distinctions that need to be made with regard to factors such as the cultural and educational backgrounds of refugees, the flow of refugees and the circumstances from which they are fleeing are rarely short-lived. Therefore, the structures and services that are put in place for dealing with refugee emergencies often produce a series of challenges that should be understood and addressed by the primary care physician who attends to refugees as patients.

Refugees arriving in the United States often face obstacles in accessing medical care. Access to healthcare for refugees is of particular importance because the circumstances under which these people fled their country may have had notably negative impacts on their physical and mental health. The family physician, who is oftentimes the first point of access to the healthcare system in the United States or in other countries, is in an important position to bridge the gaps between providing high-quality medical care, assisting them in efficiently navigating the complexities of the local healthcare system, and integrating their social environment into care plans. Other issues such as completing government or insurance paperwork, language and cultural differences, and socioeconomic difficulties are

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also important factors that contribute to difficulties in accessing healthcare [6].

Approaching the Refugee Patient

In addition to the difficulties that refugees often face during the departure, transit, and arrival stages of their journey, the family physician's approach to the refugee patient should be sure to assess for barriers to accessing or utilizing healthcare services.

Several studies have found that refugee patients and their healthcare providers cite legal, financial, and administrative processes as the greatest barriers to providing patients with healthcare services [6–9]. In the United States, only those refugees who have undergone the legal process to apply for asylum are given full access to healthcare coverage under government programming. Without an official application for asylum in the system, refugee patients are only entitled to emergency medical services. This often only compounds the patient's and family's economic strain and reduces their willingness to seek out care. While the ideal situation for these patients is waiving of the legal restraints that limit access to care, policy changes are likely a long way from implementation. Therefore, the family physician should familiarize themselves with the laws and policies in their state or country and consider advocating for needed changes that ensure equity and access to care for all people.

Language and cultural issues are also significant barriers to care for refugee patients [10, 11]. While interpretation services may be available, not every health center has access to these services [12]. Alternatively, these services may include a limited number of languages or dialects. In addition to accurate translation of language, optimal interpretative services provide a certain level of cultural mediation through limited explanations of language and expression where needed. However, even with ideal levels of interpretation, increased effort and flexibility on the part of the physician are required to understand unfamiliar cultural and linguistic nuances that may affect physician understanding, patient experience, comfort, and adherence to recommended plans of care.

Certain aspects of healthcare may come with barriers of their own that the family physician must take into account when assessing, treating, or referring refugee patients. For example, many refugees are in need of mental health services, whether for preexisting psychiatric conditions or for problems arising from the physical and psychological stressors that a refugee may have encountered on the course of their journey [12]. While studies suggest that the best way to combat mental health issues in refugee patients is to intervene as soon as possible after a patient's arrival [13], it may be a long time before the family physician comes into contact with a refugee patient. Therefore, it has been shown that approaching a patient's experience with a patient-centered, narrative approach improves their willingness to divulge psychosocial concerns and to adhere to medical advice or treatment [14].

Sexual and Reproductive Health

Quality sexual and reproductive health resources are essential to the health and well-being of refugees. As with any population, conversations and care regarding sexual and reproductive health require an understanding of the religious and cultural norms within the community [15]. For certain sexual and reproductive health screenings, procedures, or conversations, the gender of the family physician may be a barrier to providing this type of care, and flexibility on both sides may need to be negotiated. However, regardless of physician gender, some cultural groups may not be open to conversations about family planning or birth control [16, 17]. The physician may encounter patients who have been victims of female genital mutilation (FGM) or other injuries of reproductive organs. Victims of rape or sexual torture may present to the family physician and may not be willing or able to discuss their condition in a way that is conducive to treatment [18]. The healthcare team may need to partner with family members or other cultural insiders from the community who can help the physician

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develop an approach or pathway to follow when addressing sensitive topics with the community. Many refugees and immigrants are or have been victims of intimate partner violence, and the family physician should be vigilant to the language and behaviors that patients or their family members use that could point to such circumstances.

Taking a History

Understanding the patients history in phases – "pre-displacement," "during displacement/camp health," and "at/after arrival" health – is a good model to use when the patient is first encountered [13]. This model reflects the varying risks, experiences, and exposures during the different phases of the refugee experience, which can vary in type, severity, and duration.

Many refugee patients will lack appropriate medical records for themselves and/or for their children. This increases the need for the family physician take a strong, comprehensive, and detailed history from the patient to ensure appropriate continuity of care. While the medical history of a refugee should certainly consider the typical points of a history, the family physician should include or place emphasis on certain elements of the history to include infectious disease and vaccination history, chronic disease, medication and supplementation history, and mental health screening.

Mental Health and Mental Health History: Identifying PTSD, Depression, Anxiety Disorders, and Adjustment Disorders

Stigma of mental health in culture may be a barrier to eliciting symptoms or prior diagnoses of mental health issues from a patient history. In a similar vein, refugees who experience physical, mental, or sexual trauma or torture may be reluctant to include key information regarding these experiences in their history. Therefore, it is essential that the physician investigates such elements of patient history well, using a trauma-informed approach to ensure that the patient develops and maintains a trusting relationship with their healthcare provider and feels safe, comfortable, and understood for the duration of their care. The most frequently diagnosed mental health disorder in refugee populations is PTSD, commonly as a result of experiencing or witnessing violence or from the stressors of their journey to resettlement [19]. While a combination of selective serotonin reuptake inhibitors (SSRIs) and cognitive therapy has been proven highly effective in the treatment of PTSD, the lack of culturally suitable approaches to diagnosis, pharmacological treatment, and therapy often prevents optimal treatment outcomes for these patients [20]. An assessment of mental status is required as part of the screening examinations required by the Department of State and the US Citizenship and Immigration Services.

One should also consider the different but ongoing mental health stressors that refugees experience after resettlement. Even refugees that have been established in the United States for a long period of time can experience further mental trauma from racism and hostility imposed on them or their children from native citizens, economic stressors, and even social stressors that can push people toward unhealthy habits. These may include gambling or substance abuse [21, 22]. Often, refugees are separated from immediate family members and experience trauma from this separation and the additional lack of a social support network. Such traumas often fly under the radar, as they are not often emphasized in literature or screening protocols, and therefore it is important for the family physician to address these sources of mental health trauma.

Infectious Diseases

Refugees tend to be at higher risk for contracting infectious diseases at any stage of their journey, whether pre-flight, during travel, or upon arrival at a refugee camps or a resettlement city. Poorer living conditions and inadequate access to healthcare services contribute to the spread of such diseases. The etiology of infectious diseases among refugees depends on their country of

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origin, the trajectory of their journey, and other demographic characteristics that may place them at risk for certain infectious diseases [13, 23]. All refugees arriving in the United States are required to undergo a medical screening as outlined by the Centers for Disease Control and Prevention (these guidelines can be reviewed at https://www.cdc.gov/immigrantrefugeehealth/guidelines/refugee-guidelines.html). One of the major reasons for these screenings is to contain and reduce infectious diseases that may be brought into the United States. The required exams include a medical history, physical exam, chest X-ray, syphilis, tuberculosis and HIV testing, and several other specific lab tests [24]. Therefore, it is imperative that the family physician take appropriate precautions to ensure that infectious diseases are detected and treated in an efficient and timely manner. As part of the required testing for immigration to the United States, appropriate immunizations are also required.

Nutrition

Assessing dietary practices as well as concerns for food insecurity among refugee patients is an essential part of a comprehensive history for this group. In addition to economic barriers to obtaining healthy food, considerations such as cultural preferences, religious restrictions, and geographic barriers, such as residence in areas that are considered to be "food deserts," should also be taken into account.

Oral Health

A number of studies have documented poor oral health in some refugee groups [25, 26]. The importance of oral health is well-established in research and healthcare practice. The contribution of poor oral health to conditions such as diabetes, cardiovascular disease, and other health conditions in refugee populations is an important consideration for the family physician when seeing refugee patients in clinic. Many factors can contribute to the poor oral health of refugees, including but not limited to lack of knowledge or perceived importance of dental health, inevitable diet change upon arrival, time spent in camps or resettlement cities without access to dental health care, and access or lack of knowledge regarding how to access dental services once resettled. While the treatment of dental conditions falls largely outside the scope of a family physician's practice, the physician may consider implementing a program in their practice to provide refugee patients with dental hygiene equipment such as toothbrushes, toothpaste, and floss. Access to quality, affordable dental care referral sources is also important. To whom the family physician can refer refugee patients with oral health concerns is also recommended.

Trauma and Torture

The family physician should consider the possibility that refugee patients may have experienced physical or mental trauma or undergone torture at the hands of others, including military personnel or law enforcement in their country of origin or on their journey to safety. One study at an urban primary care center in the United States found that 11% of foreign-born patients had a history of torture [27]. In addition to the physical consequences of the trauma, the psychological effects of these experiences should be assessed and addressed by the family physician. These experiences are sometimes difficult to assess due to repression or minimization of the experience by the patient, whether due to psychological coping mechanisms or feelings of shame that often accompany these experiences. The family physician should consider the influence of culture in the expression of physical or psychological symptoms. While physical signs and symptoms of prior physical trauma are often obvious (e.g., scars, burns, broken bones, etc.), the psychological effects may require a more in-depth assessment by the clinician. The clinical symptoms that are displayed by patients who have experienced trauma and torture are often quite similar regardless of linguistic or cultural background. PTSD, major depressive disorder, and anxiety disorders

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are by far the most common disorders experienced by refugees and often present similarly [19]. The long-term consequences of physical injury, such as the effects of brain damage or vision loss, should not be forgotten as possible outcomes of physical trauma or torture.

The family physician should also be sure to analyze family members or close contacts of the refugee patient for signs of psychological disorders caused by trauma or torture.

Chronic Pain

Chronic pain has been reported to be relatively common among refugees. Both physical injury and psychic injury may contribute to this high rate. PTSD has been found to be linked to higher rates of chronic pain [28]. Additionally, physical pain may be a culturally sanctioned expression of psychic suffering in some communities and groups.

Chronic Health Problems

While certain health problems, such as infectious diseases, occur at higher rates in refugee patient populations, the physician should not overlook the common health problems that affect all patients. These include conditions such as hypertension, hyperlipidemia, coronary artery disease, obesity, diabetes, and asthma. Smoking rates may be higher among many refugee groups, and smoking cessation may require different approaches to be successful [29].

Addiction

Drug and alcohol abuse is not uncommon among refugee populations. Because of the physical and psychosocial trauma that many refugees have experienced, they may be susceptible to turning to substance abuse. The family physician should conduct a thorough social history that explores drug and alcohol use and carefully assess the patient for physical and psychological symptoms that may indicate a drug or alcohol problem.

Another addiction problem that may be encountered by refugees is gambling addiction. In addition to the psychosocial impact of gambling addiction on the patient and their family and community, in some parts of the world, gambling addictions have created major economic problems for refugees and refugee communities [30, 31]. Because of the community-oriented nature of many refugee families and groups, refugee communities may help to support or pay off the debts incurred by those in their communities struggling with gambling addictions, oftentimes pulling entire families or communities into debt along with them. The predatory nature of casinos and gambling clubs also contributes to the slipperiness of these slopes for refugees, providing comfortable spaces, free hot meals, and oftentimes transportation services to and from the gambling venue.

Cancer Screening

Immigrants and refugees are significantly less likely than the general US population to have undergone cancer screening or to have an awareness of risk factors or warning signs of cancer [32, 33]. The physician should have a plan when approaching patients about these screenings, and not be discouraged if initial offers are refused. This is true particularly if a strong physician-patient relationship has yet to be established. Even if cancer screenings cannot be conducted due to time constraints or lack of a physician-patient relationship, the family physician should counsel patients on risk factors and the importance of cancer screenings. The use of translator services both for language and cultural purposes is often very helpful here.

Refugee Children

Adjusting to new educational systems, social environments, and home environments is often a difficult experience for children whether or not other factors are contributing to stress. While studies show that refugee children usually adjust to their new environments relatively well, these

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children may report peer difficulties such as bullying or social exclusion in schools [34]. Such stressors can cause children to feel disconnected from their families and result in their drifting toward gangs, drug use, or alcohol abuse [35, 36]. Another consideration to be made is differing cultural practices, such as cupping or scraping in Chinese medicine, that are often mistaken as signs of child abuse by teachers, counselors, or classmates [37]. The family physician should be aware of these cultural practices and inquire about such findings with both pediatric patients and their parents.

Legal Considerations

Refugees arriving in the United States often have a very limited understanding of the US legal system. As such, they may feel unsure or unsafe about situations that might require them to report information about themselves or their families for fear that they may face legal repercussions. The patient should be assured that physician-patient confidentiality is an important element of the medical relationship and that no stage of medical intervention involves reporting immigration or immigration status to the authorities. The family physician should also be aware that many refugees find themselves in situations where landlords, employers, or businesspeople take advantage of their lack of understanding or their desperate situation. Refugees may also have a difficult time understanding how to pay bills or rent, and in these cases, the family physician should try to put refugees in touch with culturally sensitive social workers, trusted settlement agencies, or free legal clinics that can help to intervene on behalf of the patient.

Establishing a Medical Home

A 2019 study found that continuity of care was cited as the second most important factor by both healthcare providers and patients, behind language differences as barriers to providing healthcare to refugees [38]. Additional issues included the lack of availability of adequate medical records, healthcare system complexity, access to healthcare facilities, and difficulties with integration of medical appointments into the personal schedules of refugees which all contribute to the difficulties in providing continuity of care. While ensuring continuity of high-quality care is a multidisciplinary effort that requires input from primary care providers, medical specialists, social workers, legal aid, and educators, the family physician can contribute greatly to the establishment of a refugee's medical home by providing culturally competent, trauma-informed, and patient-centered care to this patient population. By doing so, the family physician can establish themselves as allies to refugee and immigrant patients, building trust between newcomers and the medical system that serves them.

Prevention and Public Health

The role of the family physician in prevention and connection of medical practice to public health infrastructure is unmatched by any other specialty in medicine. The establishment and strengthening of public health systems that target the root causes of poor health in refugee populations are essential to ensure that refugees are appropriately cared for and can integrate into and contribute to society. Screening for and treating infectious diseases, health education, vaccination, and chronic disease and cancer screenings all fall under the umbrella of the family physician's role in providing preventive and public health care to refugee populations.

Social determinants of health are a major consideration when treating refugee patients. Upon leaving their country of origin, many of these patients lost fortunes, land, belongings, and the social capital that they once had and must now exist in a new environment with new people, surroundings, and many fewer resources. Oftentimes, refugee resettlement areas (RRAs) are located in economically depressed cities or districts in the United States, exposing refugees to environmental health risks, enhanced economic challenges, and fewer social and educational opportunities. All of these public health factors must be considered in the holistic approach to the refugee patient. The family physician should

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collaborate with patients to prevent poor health outcomes by addressing or minimizing the effects of as many of these factors as possible.

Patient Education

Before patient education can be conducted, literacy levels must be established. Even when engaging with English-speaking patients, the physician must evaluate the patient's literacy level and provide advice and information in language that is clear and understandable to the patient. For most refugees, English is not their first language, and therefore, qualified translation services and appropriately translated educational materials that meet the level of language and functional health literacy of the target audience are essential. Despite this generalization, some refugees were educated in strong systems and do have high levels of education – low literacy should not be assumed but should be assessed and analyzed by the clinician to establish the need for appropriate educational resources for a patient and their family.

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Substance Use Disorders

66

Alicia Kowalchuk, Sandra J. Gonzalez, Maria C. Mejia, and Roger J. Zoorob

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Definition and Background

A substance is any legal or illegal psychoactive material used by an individual with the potential for producing negative social and health concerns. Substances may be medically prescribed (i.e., hydrocodone) or recreational (i.e., marijuana). Substance use, misuse, and use disorder are part of a spectrum as discussed below. Substance misuse can reasonably be considered a lifestyle problem that may lead to harm. Effective preventive measures exist that may significantly reduce this harm and associated cost. Prolonged, repeated use of any addictive substances at high doses or frequency (quantity/frequency thresholds vary across substances) may lead to Substance Use Disorder (SUD). Disorders can range from mild and temporary to severe and chronic [1].

SUDs are defined as the recurrent use of drugs that causes clinically significant impairment, including health problems, disability, and failure to meet major responsibilities at work, school, or home. The coexistence of both a mental health and a SUD is referred to as a co-occurring disorder [2]. The current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) combines the DSM-IV categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe. The revised substance use disorder, a single diagnosis, better matches the symptoms that patients experience, and recognizes the continuum a patient's substance use impairment may progress along with this chronic, relapsing illness [3].

This chapter will discuss substance use disorders, except for alcohol and tobacco use disorders, which are addressed in other chapters.

SUD History and Primary Care

Substance use has been viewed throughout history in various ways, including through a moral or spiritual lens, as an immoral act, or a direct action by the gods. Roman civilizations considered wine a right for every individual, while in other cultures, alcohol and other substances were completely prohibited [4]. Sigmund Freud, neurologist and founder of psychoanalysis, offered evidence from clinical observations that biological factors play a role in the addiction process. Reflecting on the influence of psychodynamic theories of etiology after World War II, the DSM-I and DSM-II emphasized those approaches in attempting to explain the addiction process. However, DSM-I and DSM-II stigmatized addiction by listing it with other society-disapproved disorders stemming from personality disorders. DSM-III and IV espoused a theoretical, descriptive diagnosis, requiring tolerance or withdrawal to diagnose dependence. DSM-IV's emphasis on biology in its concept of dependence was unchanged from its immediate predecessors. DSM-5 states that drugs taken in excess have in common the direct activation of the brain reward system [3].

Substance use, misuse, and use disorders are common in primary care patients and are a

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significant contributor to morbidity and mortality. Two key strategies to address substance use in primary care are the process of screening, brief intervention, and referral to treatment (SBIRT), and the integration of treatment for SUDs into primary care [5]. These concepts will be expanded on later in this chapter.

Epidemiology

According to the 2015 National Survey on Drug Use and Health, 20.8 million people in the USA are diagnosed with Substance Use Disorders [5]. Moreover, over 20% of patients hospitalized in general wards have SUD, and patients with SUD are 1.5 times more likely to be readmitted to the hospital [6]. Substance use disorder affects 16% of Americans ages 12 and older (40 million people). That is more than the number of people with heart disease (27 million), diabetes (26 million), or cancer (19 million) [7].

Figure 1 shows the prevalence of people aged 12 years or older with a Substance Use Disorder in the past year. This 2018 data set shows that more than two-thirds of people (14.8 million) diagnosed with SUD in the past year had an alcohol use disorder. Illicit drugs and marijuana use disorders followed the prevalence of alcohol at 8.1 million and 4.4 million, respectively [8].

The attitude of high schoolers toward the use of marijuana has changed substantially in the last two decades with more than half now considering marijuana use safe. As shown in Figure 2, marijuana remains the most used illicit drug (35.7%) in teens, followed by lysergic acid diethylamide (LSD) and other synthetic drugs [9].

The number of people with SUD is continually growing, and despite the availability of evidence-based interventions, a substantial implementation gap exists. There is a large treatment gap between those who need treatment for a SUD and those who receive it. In 2011, 21.6 million persons aged 12 or older needed treatment for an illicit drug or alcohol use problem, but only 2.3 million received treatment at a specialty treatment facility [10].

Classification

The cascade of care model was initially adapted for human immunodeficiency virus (HIV) and other communicable and noncommunicable diseases to highlight the gaps between current care and recommended treatment goals. A similar model is being studied to address treatment gap issues in opioid use disorders (OUD). With additional attention to prevention and identification stages, it could result in improved practices and

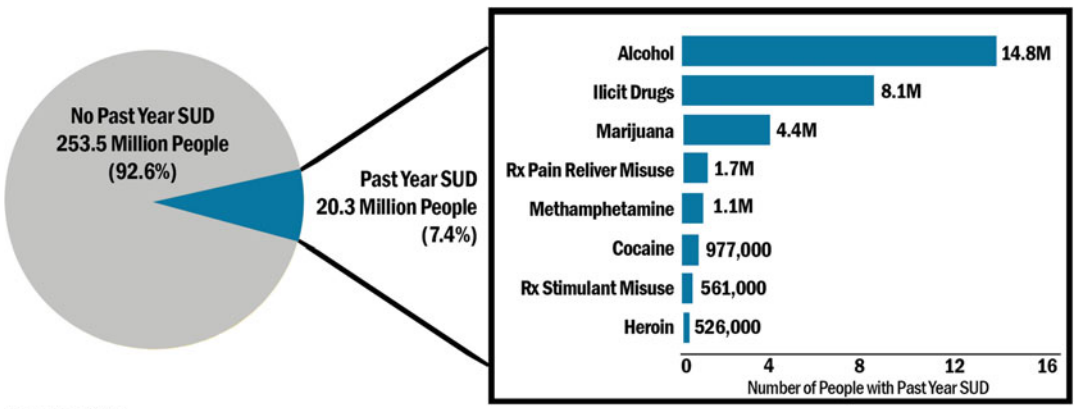


Fig. 1 Past-year substance use disorder prevalence in the USA

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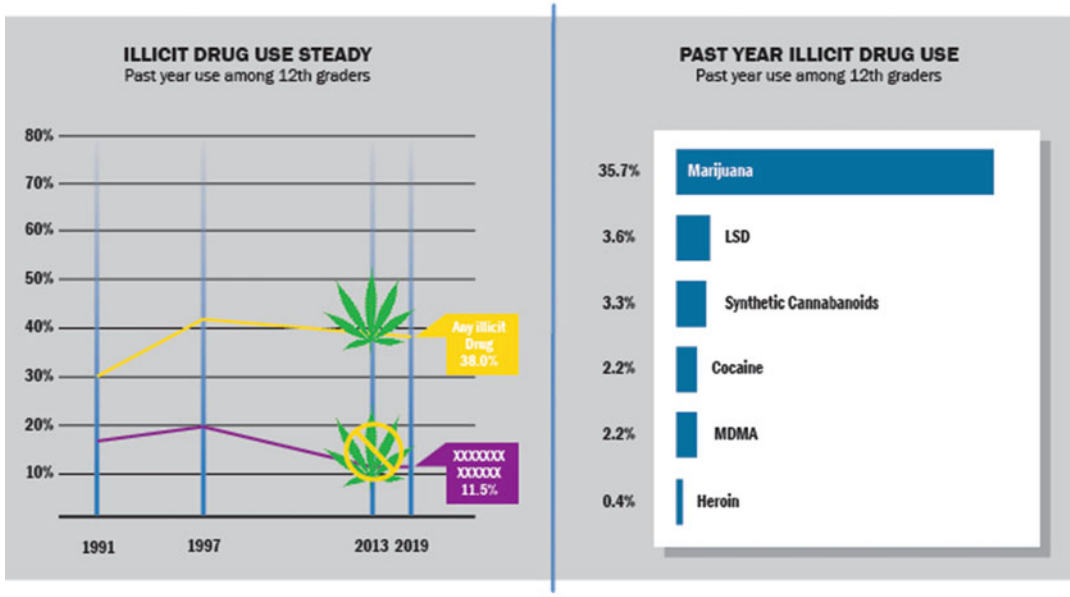


Fig. 2 Marijuana and other illicit drug use in adolescents

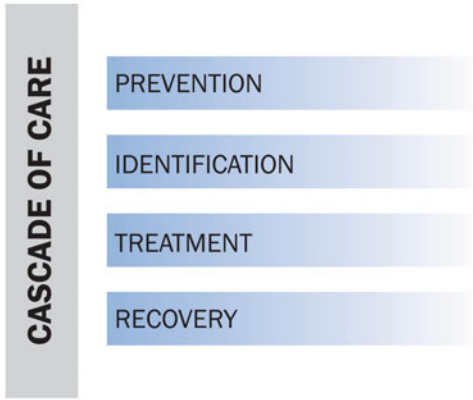


Fig. 3 National Institute on Drug Abuse Cascade of Care model recommended for opioid crisis [12]

treatment outcomes [11]. Figure 3 shows an example of this cascade of care model.

DSM-5 Criteria for Substance Use Disorders

DSM has been the standard for diagnosis and treatment in clinical, research, and administrative settings. DSM-IV, published in 1994, showed strengths in its reliability and validity of dependence. The reliability of abuse data was much lower, with nearly half of the abuse cases being diagnosed with only one criterion (syndrome requires more than one symptom). Upon further investigation, the relationship between abuse and dependence was found to be unidimensional indicating the same underlying condition. To overcome these issues and to improve diagnostic accuracy, abuse and dependence were combined in DSM-5 [13].

Two criteria, craving and consumption, were studied to increase diagnostic accuracy. While craving or "a strong desire or urge to use the substance" made it into the DSM-5 SUD criteria, consumption did not fit owing to the difficulty in quantifying illicit drug consumption. DSM-5 substance use disorder criteria were developed in 2013. Data from the general population and clinics were reviewed, and a threshold of two or more criteria was selected (with exception to supervised use of psychoactive substances for medical reasons). The criteria are based on four domains: impaired control over drug use (criteria 1–4), social impairment (criteria 5–7), risky drug use (criteria 8–9), and pharmacological effects

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on biological functioning (criteria 10–11). See the complete list of criteria below. The number of criteria a given patient meets assesses severity of their substance use disorder: mild (2–3 criteria), moderate (4–5 criteria), and severe (6 or more criteria) [14]. Patients meeting criteria for multiple substances are diagnosed with multiple distinct SUDs, for example, OUD severe and cocaine use disorder (CUD) moderate, and not polysubstance use disorder, which is not a recognized diagnosis in the DSM-5.

DSM-5 Diagnostic Criteria for Substance Use Disorders

- Used larger amounts/longer
- Repeated attempts to quit/control use
- Much time spent using
- Craving
- Neglected major roles to use
- Social/interpersonal problems related to use
- Activities given up to use
- Hazardous use
- Physical/psychological problems related to use
- Tolerance
- Withdrawal

General Principles

A chronic disease model of care has become the standard for addressing SUD, which is now recognized as a chronic, relapsing disease. Primary care clinicians and practices are well versed in chronic disease management, and inclusion of SUD in their repertoire increases access to care for patients suffering with SUD [15].

Approach to the Patient

Ensuring the office environment is stigma-free and welcoming of patients with SUD is key to effective patient engagement and includes having readily accessible print or electronic health information on SUDs in waiting areas, staff trained to use non-stigmatizing language, and screening for substance use routinely for new patients using standardized screening instruments. Stigma is a significant barrier to patients with SUD engaging with the healthcare system. See Table 1 for stigmatizing language to avoid and suggested alternative language [16].

Screening, Brief Intervention, and Referral to Treatment

Screening, brief intervention, and referral to treatment (SBIRT) is an evidence-based framework that is used to identify individuals with SUDs and those who are at risk for developing SUDs. It is a public health approach that can be implemented across a variety of settings, including primary care. The components are: universal screening, brief intervention, and referral to treatment. Current research demonstrates that SBIRT is effective in reducing harmful alcohol use and drug use in patients who do not have a substance use disorder. Screening should occur at least annually for all patients using a validated screening instrument such as the Single Question Drug Screen (SQDS). In primary care, screening can occur during the patient rooming process as performed by ancillary staff. Three-quarters of the patient population are likely to screen negative. For those that screen positive, a brief intervention based on motivational

Table 1 Avoiding stigmatizing language

Avoid (Stigmatizing)	Alternatives (Non stigmatizing)
Abuse, Addiction	Misuse, Use disorder
Addict, Abuser	Person/patient with a substance use disorder
Dirty/Clean (Individual)	Relapsed/in recovery
Dirty/Clean (toxicology result)	Test positive/negative for substances (list out)
Medication assisted treatment	Medications, SUD medication, medication for SUD, office based opioid treatment (OBOT)

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interviewing can be delivered, either by the primary care physician or a behaviorist in an integrated practice setting, to increase awareness of the risks associated with continued use and to motivate the patient to reduce or stop use altogether. For patients who may have a substance use disorder, referral to specialized treatment is warranted, if not available in the primary care office (such as with office-based opioid use disorder treatment, OBOT) [17].

Office-Based Opioid Treatment

Office-based opioid treatment (OBOT) provides buprenorphine or naltrexone medications to patients with OUD in the primary care setting to help them achieve and sustain long-term recovery. OBOT services may include on-site provision of counseling services or referral to community counseling resources.

Diagnosis

History

History of substance use and its associated impact on health and functioning are essential in making the diagnosis of SUD. While toxicology testing can indicate discrete points in time of substance use or abstinence, only a thorough history can help the clinician identify the continued use despite adverse consequences and loss of control over use that are the hallmarks of SUD. Table 2 shows the components of a comprehensive substance use history.

Additionally, current and prior relationship, employment and legal issues related to substance use, presence of cravings, and withdrawal symptoms during periods of even brief abstinence, and increasing use over time to achieve the same or diminished feelings of euphoria are important to ask about for making a SUD diagnosis using the DSM V criteria. See list of criteria above. In addition, standard past medical and surgical histories are essential for patients with SUD presenting as new to the practice. It can be helpful to focus on pertinent positive and negatives for medical and surgical sequelae of SUD including HIV, Hepatitis C, other liver or pancreas problems, heart problems such as endocarditis, and recurrent sinus infections. Family history of SUDs including alcohol and tobacco are also important given the genetic and environmental risk factors for SUD development. A complete psychiatric history is useful for establishing or ruling out co-occurring disorders, detailed later in this chapter. For the biologically female patient with SUD, an obstetric and gynecologic history is

Table 2 Components of a comprehensive substance use history

For each substance	Age at first use	Age of problematic use	Last use	Route of administration (and source of needles if injection route)	Frequency of current use (e.g. past 3 months)	Quantity (units e.g. pill count, weight or cost)
For each prior treatment episode	Date or Year	Location	Level of care (e.g., residential, outpatient, OBOT)	Length of service	Time until relapse (after treatment completed)	Relapse trigger (if known)
Mutual aid involvement	Organization (e.g. Narcotics Anonymous, SMART Recovery)	Frequency of attendance	Sponsor	Home group	Longevity (e.g. 90 days, 6 months, 4 years)	Steps completed
For each overdose episode	Person overdosed (e.g. self, friend, loved one)	Intentional vs accidental	Substance/s involved	Naloxone availability (if opioid involved)	Outcome	Link to care? (yes/no, if yes what treatment services received)

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also important especially current sexual activity, use of contraception and/or barrier protection during sexual intercourse, and last menstrual period. Care of the pregnant patient with SUD is discussed later in this chapter.

In addition to substance use history, the rest of the social history is important in determining the best level of SUD care for the patient. If a patient is living in a sober, safe home environment with at least one other supportive adult and is still actively engaged at least minimally in work, school, parenting, and/or their community, then ambulatory, primary care-based treatment options may be considered. Conversely if a patient is homeless, living with a violent or non-sober partner, living alone, and/or not engaged in other activities besides substance use and recovery from use, residential treatment and specialty care may be preferred.

Lastly, a trauma history can be helpful to elicit, particularly after establishing a strong therapeutic relationship with a patient, as there is a significant increased burden of traumatic experiences across the lifespan in patients with substance use disorder. In women with substance use disorders in residential treatment settings upward of 90% may have a history of trauma, often multiple experiences. Unaddressed trauma can play a significant role in risk for relapse, continued exposure to abusive relationships, and incidence and instability of co-occurring psychiatric conditions [18].

Physical Examination

A thorough physical exam for a patient with SUD focuses on looking for direct and indirect effects of substance use on the body. See Table 3.

Laboratory and Imaging

Laboratory testing to monitor for evidence of substance use is an important component of every treatment and management program. Testing adds structure and accountability that are critical aspects of helping patients regain self-control and self-respect, and presents an opportunity for reviewing the patient's recovery management. However, the usefulness of laboratory testing results is limited as stand-alone criteria for diagnosis of SUD. Blood, urine, and saliva studies do not measure severity of the disease or fully assess the associated physical harm. Laboratory testing is useful for initial assessment, screening to identify nonprescribed substances/medications, monitoring adherence to pharmacotherapy, evaluating efficacy of treatment, and assisting in treatment planning [19]. It is recommended that laboratory testing be random, observed, convenient for the patient, high quality, and provide timely results [19]. However, there is great variability in clinical protocols and requirements regarding laboratory testing characteristics (e.g., random vs. scheduled; observed vs. nonobserved) based on different healthcare provider settings. Urine is the most commonly used matrix due to its widespread and economical availability, sensitivity and specificity, and ability to detect substance use over periods of time useful for treatment planning. See Fig. 4 [19].

The most common clinical approach is to test for a panel of substances with high prevalence in a given community using screening tests (i.e., Enzyme immunoassay), which can be performed in a lab or using onsite point-of-care testing (POCT) kits [21]. Confirmatory testing

Table 3 Components of a comprehensive physical exam

General survey	Alertness, hygiene, appropriateness of dress for weather (e.g. long sleeves in hot weather to hide needle marks on arms), distress, restlessness
HEENT	Pupil dilation or constriction for ambient light, nystagmus, nasal septum perforation, dentition
Cardiovascular	Cardiac murmurs, arrhythmias
Pulmonary	Wheezes, rhonchi
Abdominal	Hepatomegaly, scars consistent with blunt or penetrating trauma history
GYN/GU	Abnormal discharge, rashes or sores
Extremities	Nail bed flame hemorrhages, edema
Neuro	Alertness and orientation, tremors, ataxia
Skin	Needle marks, abscesses, tattoos, rashes e.g. scabies or other skin infestations

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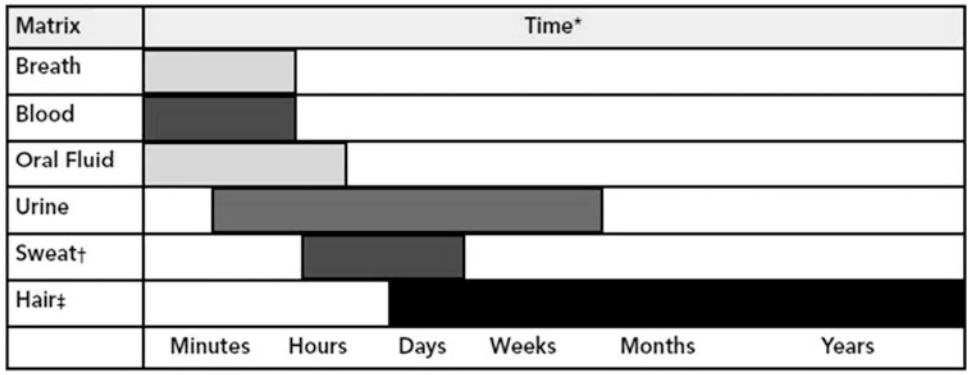


Fig. 4 Laboratory test matrices to detect substance use

(i.e., chromatography with spectrometry) should be performed only for positive results whose accuracy is important for treatment planning as it is not necessary in every case [19, 20]. Screening tests are often qualitative while confirmatory tests are often quantitative. In addition, quantitative results may be helpful for some significant false-positives (THC, alcohol, and cocaine). Synthetically crafted opioids (i.e., opiates) will not be detectable on a routine opioid screen, but will be identified with chromatography or spectrometry. A toxicology screen with the specific agent identified should be ordered if there is a clinical concern for misuse of an undetectable substance. No screen or labs are available to identify inhalants, except for hair analysis, which is rarely used. A thorough, confidential history is the most effective way to screen and diagnose SUDs.

Other laboratory studies should be considered based on clinical findings or concerns including a comprehensive metabolic panel, complete blood count, thyroid stimulating hormone (TSH), free thyroxine (fT4), urinary analysis, gamma-glutamyl transpeptidase (GGT) for suspected alcohol misuse, and human chorionic gonadotropin (HCG) for women of reproductive age to rule out pregnancy. If engaging in risky behavior (e.g., unprotected sex, injection drug use) is suspected, test for gonorrhea, chlamydia, HIV, syphilis, hepatitis C, and hepatitis B (if not vaccinated). Risk factors for tuberculosis should be considered and tuberculin purified protein derivative (PPD) placed if concerned.

Imaging

A 12-lead EKG should be obtained in those with chest pain associated with known or suspected stimulant use (e.g., cocaine, methamphetamine, 3–4 methylenedioxymethamphetamine (MDMA)) due to the risk of myocardial infarction. Extensive inhalant misuse is associated with cardiomyopathies. Echocardiography is indicated to identify intracardiac vegetations in patients with known or suspected injection drug use presenting with a new heart murmur.

Genetic Testing

Genetic testing for individuals with SUDs currently has little clinical value and is not recommended [21].

Special Testing: Adolescents

Laboratory screening for substance use among adolescents may be useful when assessing situations of concern at school or in accidents, domestic violence, or other trauma. Obtaining laboratory testing without the consent of the competent adolescent can hinder the physician–patient relationship and should only be done in emergent situations [22]. Failure to do so also causes legal consequences for the physician as substance use

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disorders are frequently on the list of conditions along with pregnancy and family planning for which adolescent minors have legal right of consent, with age of legal consent determined by state law. In general, drug screens should not be performed solely at the request of parents because the clinical information yielded from such testing is limited. False-positive results are common and can have significant medical and social consequences [20].

Differential Diagnosis

While acute intoxication and withdrawal syndromes can mimic other medical and mental health emergencies such as hypoglycemia, thyroid storm, and acute psychotic or manic episode, a thorough history taken when the patient is not severely intoxicated or withdrawing is typically sufficient for making a SUD diagnosis. More common are co-occurring psychiatric disorders, including bipolar disorder, other mood disorders, post-traumatic stress disorder, attention deficit hyperactivity disorder, and personality disorders. Figure 5 shows the 2018 prevalence of past year SUD and mental illness for US adults [8].

Mood disorders are the most common co-occurring psychiatric disorders in patients with SUD. Conversely patients with mood disorders have a lifetime SUD prevalence of 32%. For patients with bipolar disorder that increases to 56%. A thorough psychiatric history is indicated in patients with SUD and vice versa to avoid missing these commonly comorbid conditions, as an untreated co-occurring disorder makes achieving and sustaining SUD recovery much more difficult [23].

Treatment

Behavioral

Cognitive behavioral therapy (CBT) for substance use disorders focuses on identifying and modifying maladaptive thoughts and patterns of behavior that reinforce or enhance substance use. It is a relatively brief and directive approach that teaches patients to understand the relationship between their thoughts, feelings, and behaviors. Cognitive strategies include cognitive restructuring, which involves examining the accuracy of thoughts and developing responses that are more likely to support desired behavior (e.g., abstinence, use of adaptive coping). Behavioral strategies assist the patient in building the skills necessary to reduce use (i.e., refusal skills). CBT can be used as a monotherapy or in combination with other treatment strategies, including pharmacotherapy when indicated [24]. Its efficacy is established in the treatment of cannabis, opioids,

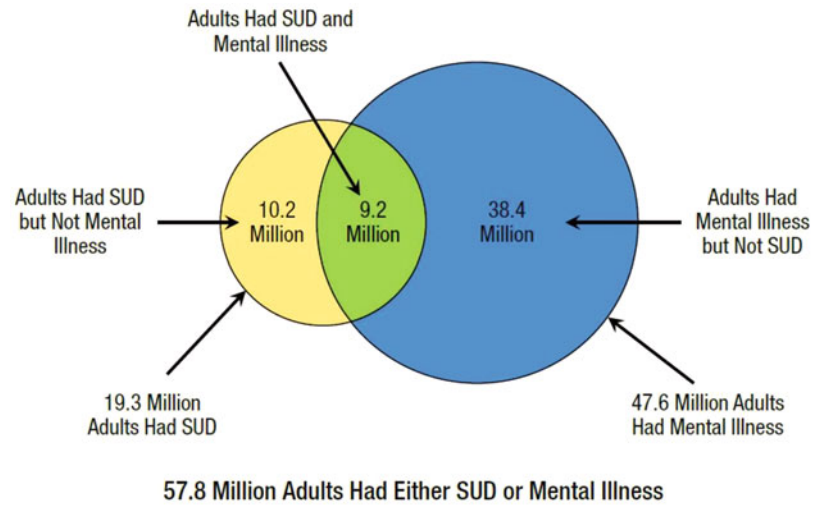


Fig. 5 Past year SUD and mental illness among US adults

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and cocaine use disorders. Since many individuals experiencing substance use disorders may also have comorbid mental health diagnoses, there are aspects of CBT that can address underlying triggers such as anxiety during social situations.

Motivational enhancement therapy (MET) is a counseling approach that assists patients in evoking intrinsic motivation for change and resolving ambivalence about substance use. It uses the tenets of motivational interviewing to strengthen motivation through a series of conversations to elicit the patient's reasons for sustaining substance use and reasons for stopping use [25]. MET consists of an initial evaluation session followed by two to four subsequent sessions focused on exploring substance use, eliciting change talk (i.e., language expressed by the patient as an argument for change), developing a plan for change, and identifying coping strategies. MET is tailored to the needs of the person receiving treatment and encourages autonomy in decision making. MET can be used as a part of an overall treatment approach which may include 12-step programs and CBT. This treatment approach has demonstrated efficacy in the treatment of alcohol, marijuana, and nicotine use disorders.

Dialectical behavior therapy (DBT), originally developed to treat patients with borderline personality disorder and suicidal thoughts, has been increasingly incorporated into SUD treatment. Similar to CBT, DBT is based on the belief that unhelpful or unhealthy thoughts and behaviors are learned and reinforced. Recognizing the limitations of traditional CBT in the treatment of challenging conditions, including SUDs and co-occurring SUD and personality disorders, DBT adds validation/acceptance and dialects to the treatment modality [26]. Many patients with SUDs have a history of trauma, which has resulted in emotional vulnerability that manifests as strong, dysregulated emotion that is reinforced by invalidating environments, i.e., consistently being told or made to feel as though their feelings are not valid. These experiences of invalidation may result in emotional unavailability, often leading to avoidance or escape which is facilitated by the use of substances. *Dialectical* refers to the synthesis of both acceptance and change with regard to the individual's use. An important aspect of DBT for substance use is the immediate expectation of a time period of abstinence, defined by the patient, which requires ongoing assessment and a renewal of commitment. DBT is a comprehensive approach which involves group and individual therapy, phone coaching, and DBT therapist consultation.

Twelve-step facilitation (TSF) therapy is a manualized treatment approach based on the principles of 12-step programs such as Narcotics Anonymous (NA). Originally developed as an individual intervention, it has now been adapted for use in group therapy. Individual treatment consists of 12–15 sessions intended to increase the patient's engagement in 12-step mutual-help organizations [27]. The approach is based on the concept of SUD as a spiritual and medical disease and has been shown to be effective in the treatment of alcohol use disorder. It has also demonstrated promising results with other SUDs. TSF utilizes the core principles of NA and encourages patients to make changes to their social networks in order to achieve and sustain abstinence.

Contingency management (CM) involves the use of rewards to reinforce desired behaviors such as abstinence. Patients may receive tangible rewards such as vouchers or cash prizes [28]. It has been shown to promote abstinence from alcohol, stimulants, opioids, marijuana, and nicotine. CM may be used as a stand-alone treatment or in combination with CBT, MET, or medication management.

Medications/Immunizations and Chemoprophylaxis

Medication Treatment: The use of medications to treat SUDs can be combined with behavioral therapies to provide a comprehensive approach to care. There are Food and Drug Administration (FDA)-approved medications to treat tobacco, opioid, and alcohol use disorders. For benzodiazepine and barbiturate use disorders (BUD), medically supervised withdrawal management is standard of care to prevent seizures and other

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potentially life-threatening complications. There are currently no FDA-approved medications for cannabis, stimulant, and other substance use disorders, and behavioral treatments remain the treatments of choice for these disorders.

Substance withdrawal is often accompanied by unpleasant symptoms that can be managed with medications as a first step in the process of recovery. Medically supervised withdrawal treatment protocols vary according to substance(s) used and symptoms present. Potentially harmful side effects can occur with acute withdrawal from benzodiazepines, barbiturates, and opioids, and withdrawal under medical supervision is preferred for adult patients with these SUDs. It is also recommended for adolescents that meet criteria for OUD and/or BUD and who display symptoms of physical dependence. BUD withdrawal is typically done in an outpatient or ambulatory setting. OUD is rarely well tolerated outside of the residential or inpatient setting, and even then relapse is common without ongoing medication support.

Opioids: Withdrawal may begin 8–24 h after short-acting and up to 36 h after long-acting opioid use. The Clinical Opiate Withdrawal Scale or COWS [29] can be used to document the patient's opioid withdrawal symptoms, see Fig. 6. Non-opioid medications commonly used for the mitigation of withdrawal symptoms to facilitate abrupt discontinuation of opioids in adults are listed in Table 4 [30, 31].

Relapse Prevention and Medication Maintenance: Due to high risk of accidental overdose and death after withdrawal from opioids or from continued opioid use, medication therapy is the standard of care for OUD. Methadone (full mu agonist) and buprenorphine (partial mu agonist) are long-acting opioid receptor agonist/partial agonist, respectively, that reduce opioid withdrawal symptoms and cravings. Methadone and buprenorphine have similar effect during opioid withdrawal, although buprenorphine is associated with less sedation and respiratory depression.

Naltrexone is a competitive antagonist at the mu and kappa opioid receptors that blocks the effects of opioids at their receptor sites in the brain and should be used only in patients who have already been medically withdrawn or otherwise off all opioids for 14 days. The monthly depot injectable formulation (XR-NTX) has shown similar efficacy to buprenorphine and methadone treatments for OUD relapse prevention, with the caveat of treatment retention which can be lower with XR-NTX [32].

Buprenorphine: Patient needs to be in mild to moderate withdrawal to start the medication, i.e., COWS >8, to prevent precipitated withdrawal. It is usually well tolerated. Common adverse effects include sweating, constipation, headache, and nausea, and are typically mild and self- limiting except for constipation. Buprenorphine/naloxone combination has less potential for diversion and overdose and is preferred over buprenorphine monotherapy for most treatment options (except pregnancy and lactation) [33, 34]. Preliminary studies of its safety and efficacy in adolescents are encouraging. Expanding OBOT to the primary care setting was the main driver for FDA approval of buprenorphine and buprenorphine/naloxone as schedule III medications. Physicians prescribing buprenorphine products for treatment of OUD must first obtain a Drug Enforcement Agency (DEA) waiver by completing 8 hours of training (free and online training programs available), and completing a brief, online registration process through the DEA's website. Additionally, there are caps on number of patients each physician may have in active treatment, based on length of time the physician has been waivered. See the Providers Clinical Support System website, https://pcssnow.org/, for additional information and resources in becoming an OBOT provider. Table 5 shows buprenorphine products FDA approved for OBOT.

Methadone: Methadone maintenance therapy for relapse prevention may only legally be provided through a licensed opioid treatment program (OTP**),** not in the primary care setting. For medically supervised withdrawal such as in the hospitalized patient with OUD, there is no need to have specific level of withdrawal to start, however, it is not recommended to start when the patient is intoxicated. The starting dose is 20–30 mg, which may need to be increased 5–10 mg to alleviate withdrawal symptoms. Dose decreases of greater than

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Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

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Fig. 6 Clinical Opiate Withdrawal Scale (COWS)

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Table 4 Non-opioid medications used in the treatment of opioid withdrawal

Medication	Target symptom	Dose
Alpha 2 agonist: **clonidine**	Increased pulse rate and blood pressure, anxiety, piloerection, aches, rhinorrhea, lacrimation, temperature dysregulation, diaphoresis	0.1–0.2 mg orally every 4 h up to 1 mg/day; hold dose if blood pressure <80 mm Hg systolic or <50 mm Hg diastolic; by day 5, start to decrease dose by 0.2 mg/day
Alpha 2 agonist: **lofexidine**[a]		Three 0.18 mg tabs 4 times daily up to 2.88 mg (16 tablets)
Hydroxyzine	Anxiety	25–50 mg orally up to three times daily as needed
Gut-acting opioid: **loperamide**[b]	Diarrhea	4 mg orally initially, then 2 mg as needed for loose stools, up to 16 mg/day
NSAID: **naproxen**	Bone, muscle, joint, or other pain	500 mg orally twice daily as needed (take with food)
Prochlorperazine	Nausea and vomiting	5–10 mg orally every 4 h as needed
Ondansetron	Nausea and vomiting	8 mg orally every 8 h as needed
Trazodone	Insomnia	100–200 mg at bedtime as needed

[a]FDA approval in 2018, used in Europe for years. Shown to produce more rapid resolution of symptoms, less hypotension, and retain people longer than clonidine [30]
[b]Use diphenoxylate/atropine if increase in self-treatment with loperamide – QT prolongation, Torsades de pointes [31]

Table 5 FDA approved buprenorphine products for OUD

Drug	Route	Formulation	Recommended once-daily maintenance dose
Buprenorphine			
Generic	Sublingual tablet	2, 8 mg	Target: 16 mg Range: 4–24 mg
Probuphine (Titan)	Subdermal implant	74.2 mg	4 implants for 6 months
Sublocade (Indivior) extended-release	Subcutaneous injection	100 mg/0.5 mL and 300 mg/1.5 mL	300 mg monthly for the first two months then 100 mg monthly
Buprenorphine/Naloxone			
Generic	Sublingual tablet	2/0.5, 8/2 mg	Target: 16/4 mg Range: 4/I–24/6 mg
Suboxone (Reckitt Benkiser)	Sublingual film	2/0.5, 4/1, 8/2, 12/3 mg	Target: 16/4 mg Range: 4/1–24/6 mg
Zubzolv SL (Orexo)	Sublingual tablet	1.4/0.36, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg	Target: 11.4/2.9 mg Range: 2.9 0.71–17.2/4.2 mg
Buna vail (Biodelivery Sciences)	Buccal film	2.1/0.3, 4.2/0.7, 6.3/1 mg	Target: 8.4/1.4 mg Range: 2.1/0.3–12.6/2.1 mg

5 mg every several days are not well tolerated. For hospitalized patients with OUD already enrolled in an OTP, their methadone dose should be continued while hospitalized.

Naloxone for Opioid Overdose Prevention: Naloxone is an opioid antagonist used in opioid overdoses to counteract life-threatening depression of the central nervous system and respiratory system, allowing an overdose victim to breathe normally. Naloxone is a nonscheduled (i.e., non-addictive), prescription medication. Increasing awareness and availability of naloxone is a key part of the public health response to the opioid epidemic. Patients receiving long-term opioid therapy, including opioids for cancer and non-cancer-related chronic pain as well as OBOT, should be co-prescribed naloxone in case of accidental overdose [35].

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Benzodiazepine and Barbituate Withdrawal: After discontinuation of a therapeutic daily dose used for 4–6 months or a dose exceeding 2–3x the upper limit of therapeutic dose used for 2–3 months, symptoms of withdrawal begin 12–48 h after last use, depending on drug used. BUD withdrawal seizures can occur up to 2 weeks after discontinuation. The Addiction Research Foundation clinical institute withdrawal assessment for alcohol scale (CIWA-Ar) [36] is used to assess the severity of signs and symptoms of BUD withdrawal. Substituting a different benzodiazepine than the patient's benzodiazepine of misuse or phenobarbital with scheduled tapering is standard of care for medically managed withdrawal of BUD. The CIWA-Ar is helpful for monitoring and adjusting tapering intervals and percentages. Dose reduction is recommended of no greater than 25% per week initially, and 10% weekly is often better tolerated particularly after initial dose has been decreased by 50% [37]. Other adjunctive medications are listed in Table 6. Withdrawal-related anxiety symptoms and recurrence of underlying anxiety disorders should be anticipated.

Abscesses from injections and related conditions should be treated. HIV, hepatitis B and C, and other infections should be ruled out or treated. Up to date immunization schedule should be assessed and provided based on patient risk factors.

Referrals

One of the most commonly used resource for placement, continued stay, transfer, or discharge of patients with addiction and co-occurring conditions is the American Society of Addiction Medicine (ASAM) Placement Criteria [38]. The criteria are required in over 30 states to guide the nomenclature for describing the continuum of addiction services. The levels of care consider patient's needs, obstacles, and liabilities, as well as their strengths, assets, resources, and support structure to determine the appropriate level of care. It encompasses four broad levels of service and an early intervention level (0.5, 1, 2, 3 4). Within the five broad levels of care, decimal numbers are used to further express gradations of intensity of services.

Outpatient Services: Outpatient services are organized services that may be delivered in a wide variety of settings. Standard outpatient care comprises less than 9 hours of service/week for adults, or less than 6 hours a week for adolescents for recovery or motivational enhancement therapies and strategies. Intensive outpatient treatment programs (IOP) deliver 9 or more hours of treatment service a week for adults or 6 or more hours for adolescents. IOPs typically offer programming during the day, before or after standard business hours, evenings, and/or on weekends to accommodate clients' work, school, and caretaking responsibilities.

Residential Services: Residential services range from low-intensity, sober living with peer support structured accountability services, to medium and high intensity treatment services. Treatment services are provided by licensed counseling and (for high intensity) medical staff providing addiction, mental health, medication management, and general medical services in a structured program with 24-h living support. Some specialized residential treatment services for women support their children as well offering day care, transportation to local public school for school aged children, parenting classes, and play therapy. Most residential treatment programs offer aftercare support as well with peer recovery

Table 6 Adjunctive medications for benzodiazepine withdrawal management

Medication	Target symptom	Dose
Hydroxyzine	Anxiety	25–50 mg orally every 6–8 hours as needed
Buspirone	Anxiety	10 mg orally every 8 hours
Carbarnazepine	Reduce withdrawal symptoms and promoted abstinence	200–800 mg/day orally during and after taper
Trazodone	Insomnia	100–200 mg orally at bedtime as needed
Melatonin	Sleep quality	6–10 mg orally before bedtime as needed

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coaches engaging with and providing peer support to program clients for several years after graduation, and with structured programming for alumni and their families.

Mutual Aid Programs: This is one of the most easily accessible models of recovery support, though not considered formal treatment. Twelve-step programs are the most well-known of these models, i.e. Narcotics Anonymous, and are peer run self-help meetings where participants admit past mistakes, surrender to a higher power, and learn how to cope with their SUD, avoid triggers, and live sober lives. Patients who complete formal IOP and residential treatment programs, particularly those using the TSF counseling modality, often continue participating in meetings, because the 12 steps help them build and sustain a sober community and offer safe, sober social opportunities. These programs may also serve as a source of support for individuals who are waiting for formal treatment slots to open up. These programs are free and widespread in urban, suburban, and rural communities across the globe.

Patient Education and Activation

The Treatment Referral Routing Service or SAMHSA's National Helpline, 1-800-662-HELP (4357) or TTY: 1-800-487-4889, is a confidential, free, 24-h-a-day, 365-day-a-year, information service, in English and Spanish that provides referrals to local treatment facilities, support groups, and community-based organizations.

The National Institute on Drug Abuse (NIDA) website for patients and families offers information for people struggling with substance misuse and SUD, as well as resources for their families and friends (https://www.drugabuse.gov/patients-families).

Community Issues: Prevention from a Community Perspective

Opioid Overdose Prevention: A key aspect of opioid overdose prevention is to improve opioid prescribing. Healthcare and community leaders and experts can provide education to prescribers about the risk associated with opioid medication, providing guidelines about when to prescribe and how much, for how long. Additionally, state-level interventions such as the use of Prescription Drug Monitoring Programs (PDMP) can be used to inform prescribing decisions. Guidelines for prescribing opioids for chronic pain can be found at www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.html.

Recovery-Oriented System of Care (ROSC): A ROSC is "a coordinated network of community-based services and supports that is person-centered and builds on the strengths and resiliencies of individuals, families, and communities to achieve abstinence and improved health, wellness, and quality of life for those with or at risk of alcohol and drug problems" [39].

A ROSC is comprised of the substance use disorder treatment community in partnership with other community stakeholders including those providing mental health and primary care services to form a system of care. Together, the system of care addresses prevention, early intervention, treatment, continuing care, and recovery. Not only does the ROSC include individuals living with SUDs, it also engages family members and the community in identifying ways to improve the quality of services and increase access to those services. Substance use is addressed along the spectrum from misuse to chronic conditions and includes prevention approaches such as community education and awareness campaigns. Inherent to the model is the belief that recovery can be achieved through several pathways and that there is room to combine alternative therapies (e.g., peer recovery coaching, acupuncture, music, and art therapy) with traditional treatment. An important function of the ROSC is to provide recovery support services (RSS). Recovery support services are non-clinical services that support recovery and encompass a wide range of social services, legal services, mutual aid groups, and the use of peer recovery coaches. Peer recovery coaches are persons with lived experience of recovery who can provide emotional support as well as guidance and assistance in accessing community resources,

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employment, and making connections within the recovery community.

Special Populations

Pregnant Women: As frontline healthcare professionals, primary care providers are in an ideal position to screen, counsel, and facilitate or initiate treatment for pregnant women who are using substances. Although most women stop the use of substances once they are pregnant, many do not and those who do may resume use after the pregnancy. A key aspect of providing care to women who are using substances or may have a SUD is to employ a nonjudgmental approach that invites women to discuss their use in an open manner, thus reducing the stigma. The gold standard treatment for pregnant women with OUD is the use of opioid agonist medication, such as methadone or buprenorphine [40].

Lesbian, Gay, Bisexual, Transgender, Queer (LGBTQ): Members of sexual minority groups are more likely than their heterosexual counterparts to experience a substance use disorder during their lifetime. Although research is limited regarding the experiences of LGBTQ individuals in treatment, it appears that treatment programs that offer specialized groups for LGBTQ patients demonstrate better outcomes than those that do not. Despite this, few programs have specialized services [41]. When working with LGBTQ patients, it is important to recognize how their unique experiences, particularly discrimination, internalized homophobia, and family rejection, may have contributed to initiation of use as a coping strategy. Screening for comorbid mental health conditions is also important, as comprehensive treatment for both conditions is essential to long-term recovery.

Adolescents: Nearly half of all high school seniors in the US report using an illicit drug at least once in their lifetime. After alcohol and tobacco, the most commonly used drug is marijuana. The use of other substances appears to be related to age, where younger adolescents may use inhalants, older adolescents are more likely to use prescription medications such as opioids and stimulants. Treatment options vary based on the substance being used, length and amount of use, and severity of symptoms. In general, it is recommended that adolescents receive both individual and family therapy. Evidence-based interventions for SUDs include CBT, MET, and multidimensional family therapy (MDFT).

Older Adults: Substance use disorders in individuals over the age of 50 are on the rise, nearly doubling over the past decade and a half. Older adults tend to misuse alcohol, prescription and over-the-counter medications, and marijuana [42]. Routine screening practices, using validated instruments, can help to identify problematic use and creates an opportunity to deliver a brief intervention (i.e., a short conversation aimed at motivating a person to make changes regarding their substance use behavior) or facilitate referral to treatment.

Racial/Ethnic Minorities: The use of substances by African Americans and Hispanics is very similar to that of non-Hispanic Whites. However, African Americans and Hispanics are less likely to complete treatment and more likely to have poor treatment outcomes. In addition to socioeconomic barriers, implicit discrimination by healthcare providers is also considered a variable in treatment completion [43].

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Part XIV

Nervous System

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Headache

67

D. Garcia and Faraz Ghoddusi

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General Principles

Definition

Headache refers to pains in any location in the head and is typically described as a symptom or syndrome. A headache may be a manifestation of a variety of pathologies and can take a variety of

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forms and descriptions ranging from ice pick like in intensity and locality to a dull, pounding unilateral throbbing and to a viselike pressure grip of the entire cranium. Because the possibilities range from a benign, tension type headache to the imminently deadly subarachnoid hemorrhage, the seemingly simple complaint of "my head hurts" requires careful attention to patient history and physical examination.

Thankfully, the majority of headaches are non-serious in nature, and most are very amenable to treatment. Attentive evaluation distinguishes the life-threatening headaches from benign, yet bothersome, headaches. With this evaluation, the family medicine physician is equipped to appropriately and precisely treat this common patient complaint.

Epidemiology

It is hard to understate headaches' impact on humanity. In the year 2016, an estimated three billion people, or about 50% of the world's adult population, were thought to have suffered from either a migraine or tension-type headache [1]. Worldwide, tension-type and migraine headaches were the third most prevalent and sixth most prevalent disease. Second only to low back pain, migraine headaches were the most disabling in terms of life years spent with a disability [2].

In the Americas, migraine and tension-type headaches account each for approximately 28% of all headaches. 17% of headache sufferers have a combined migraine and tension-type headache. All secondary headaches (trauma, vascular pathologies, infections, tooth pain, etc.) account for an estimated 14% of headaches. Medication overuse headaches (MOHs) account for 10% of all headaches. Cluster headaches account for about 3% [3]. Figure 1 details the relative ratios of different headache types. Within the USA, headaches are responsible for 1% of all outpatient visits [4].

Headaches afflict males and females rather differently depending on subtype. Likely due to the hormonal differences, females are afflicted three times as often as males with migraines [3]. The rarer cluster headache, on the other hand, afflicts males three times more frequently than females [4]. Tension-type headaches (TTH) have a slight female predominance of about 5:4 [5]. Due to the higher prevalence of both migraine and TTH, females tend to suffer more frequently from headaches than males. Therefore, it is unsurprising that medication overuse headaches afflict females more frequently than males [6].

Classification

The International Classification of Headache Disorders is the mainstay of classifying headaches. In its third edition, this classification system subdivides headaches into three broad categories and over 300 subcategories [7]. The three broad categories are primary headaches, secondary headaches, and painful cranial neuropathies (see below list). For the sake of simplicity, this chapter divides all headaches into primary and secondary causes by rolling in painful cranial neuropathies into secondary headaches. The distinctive category names of "primary" versus "secondary" are largely attributed due to prevalence as opposed to any substantive differentiation in underlying pathology.

Primary and Select Secondary Headache Etiologies
Primary Causes
Cluster headaches
Migraine headaches
Tension-type headaches
Secondary Causes
Brain aneurysm
Brain tumor
Chiari malformation
Dehydration
External pressure
Ophthalmic pathology
Hypertension
Infections (brain, ear, sinus, etc.)
Medication overuse headaches
Meningitis
Stroke
Toothache
Temporomandibular joint Disorder
Trauma

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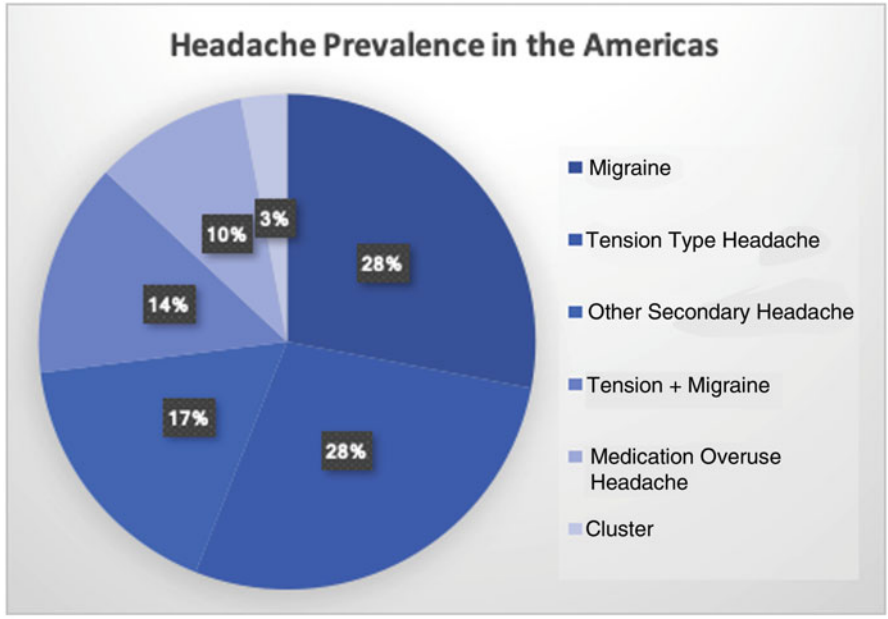


Fig. 1 Headache prevalence in the Americas [3]

Approach to the Patient

Diagnosis

General Interview Principles

Determining the headache type is almost completely dependent on history [8]. A proper headache history encounters some unique linguistic challenges. On one hand, patients will often label any severe headache a migraine, when the real culprit may be something else. On the other hand, despite the high incidence of formal medication evaluation of headache in the USA, many patients reporting migraine symptoms do not appear to be properly diagnosed with migraines [9]. Thus, the physician must carefully sift the patient's history for clues to determine the type of headache. For instance, if headache and nausea are present in the history, the patient likely does suffer from a migraine [10]. Similarly, if the patient reports headache and fever, an infection or nonvascular intracranial disorder is more likely than migraine [11].

Key facets in identifying headaches include evaluating temporal features (headache onset, duration, number of headache days per week), pain characteristics (location, quality, radiation), and precipitating and/or provoking factors. Moreover, the astute physician also explores associated symptoms such as vision abnormalities, positional changes, and other secondary body symptoms. Family headache history can often be helpful in determining the diagnosis as well. If the patient has been professionally diagnosed with a headache, discussing the changes over time can be particularly useful in directing treatment and discussing prevention strategies. To aid in diagnosis, it may be helpful to have patients catalogue their headaches along with associated symptoms on a headache diary. See Fig. 2

Finally, certain headache features are reassuring and can be used to counsel the "worried well" patient (see below).

Low-Risk Headache Characteristics
• <50 years of age
• Similar headaches in the past
• No new neurologic exam findings

Criteria adapted from Edlow et al. [12]

Conversely, specific headache features, referred to as red flags, merit special attention as

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Full Name:_____
Phone number:_____
Date of Birth: _____/_____/_____

Headache Diary

Please complete a headache diary for 1 week (or 7 headaches). Under type of pain, list where the pain is located and any other describing words like pounding, vice grip or crushing. Regarding triggers, think back about an hour prior to the headache start. Was there anything unusual you ate or drank? What were you doing? This info can provide helpful clues about ways we might prevent headaches in the future. Regarding other problems, did you have other problems while suffering from the headache?

Date	Headache length of time	Type of pain	Triggers prior to headache? Other problems?	Nausea Y/N	Sleep time previous night
/ /					
/ /					
/ /					
/ /					
/ /					
/ /					
/ /					

Other Notes: _____
_____
_____
_____
_____

Once complete please return to the Family Medicine Health Clinic. We will contact you after reviewing this diary. Thanks for trusting us with your health!

Fig. 2 Sample headache diary

they may herald more nefarious disease and serve as indicators that more diagnostic evaluations may be necessary. To aid in diagnostic discovery, and to differentiate primary from potentially dangerous secondary headaches, neurologists developed the helpful mnemonic, SNNOOP10, to recall important red flag symptoms (see Table 1).

If the physician identifies red flags, further workup targeted at specific etiology may be appropriate. A comprehensive discussion of secondary headache causes and their evaluations is outside the scope of this chapter. This chapter will limit discussion to the primary headaches and, only the most prevalent secondary headache, medication overuse headache (MOH).

Patient History

Migraines

Migraines are characterized by unilateral and pulsatile pain lasting hours which tends to worsen with physical activity. Migraines are sometimes, but not necessarily, preceded by a heralding neurologic

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Table 1 SNNOOP10 Mnemonic for Secondary Headache Etiologies

Mnemonic memory aid		Pathology
S	Systemic symptoms such as fever	Infection (meningitis, carcinoid, pheochromocytoma)
N	Neoplasm history	Primary brain neoplasm or metastasis
N	Neurologic deficit or dysfunction	Stroke; brain abscess; infection
O	Onset of headache is abrupt/sudden	Subarachnoid hemorrhage
O	Older age (after 50 years)	Neoplasm; vasculitis
P	Positional headache	Intracranial hypertension or hypotension
P	Precipitated by sneeze/cough/exercise	Chiari malformations; posterior fossa malformations
P	Papilledema	Intracranial hypertension; primary brain neoplasm or metastasis
P	Progressive headache and atypical presentations	Primary brain neoplasm or metastasis
P	Pregnancy or puerperium	Post spinal tap headache; preeclampsia, cavernous sinus thrombosis; hypothyroidism; anemia or diabetes
P	Painful eye with autonomic features	Posterior fossa, cavernous sinus, pituitary region pathology; ophthalmic primary source
P	Posttraumatic onset of headache (within 7 days)	Subdural hematoma; traumatic brain injury without hematoma
P	Pathology of the immune system (HIV)	Opportunistic infections
P	Painkiller overuse or drug side effect	Medication overuse; idiopathic drug reaction
P	Pattern change or new headache onset	Neoplasm, intracranial pathology, or vascular disease

Adapted from [11]

phenomenon known as an aura. The presence of an aura helps make the diagnosis given its high specificity for migraine headaches. An aura is a prodrome of neurologic paresthesia, classically described as a visual disturbance which precedes the development of head pain. Visual phenomena represent the most common type of aura present in 90% of patients afflicted by migraine with aura [7], but clinicians should note that other possible aura symptoms could afflict sensory, speech, motor, or brainstem neurologic symptoms. The phenomenon can be positive/additive (i.e., extra items in visual field) or negative/subtractive (i.e., partial or complete visual loss), and they are, by definition, fully reversible. Because aura symptoms (particularly dysphonia) can be extremely disconcerting, exploring aura consistency with past headaches helps avoid unnecessary repetitive workup. Thus, if a patient reports a consistent aura of left eye vision loss, repeat imaging is likely unnecessary for each subsequent similar presentation. Suffice it to say, if the aura has been present and was fully reversible in the past, this likely represents a repeat episode and not necessarily a stroke. However, if, in the same patient, the "aura" changes and is now a right-sided visual loss, imaging may be warranted.

A helpful mnemonic, POUNDing (as in headache), helps providers make the diagnosis of migraine, with the likelihood of diagnosis increasing with every positive finding after the second [13]. Similarly, the symptom triad of nausea/phonophobia/pulsation or nausea/photophobia/worsening with exertion all has likelihood ratios of 5 or greater [10]. Of all single symptoms, nausea when combined with other headache symptoms is useful for differentiating migraine from other subtypes.

Migraine POUNDing Mnemonic [13]
• Pulsating
• Duration of 4–72 h
• Unilateral
• Nausea
• Disabling

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Tension-Type Headaches

Unfortunately, the other primary headaches aren't as distinctive as migraine headaches and have less specific findings. Tension-type headaches tend to be a dull and more of a diffuse, mild to moderate pain described as a "band wrapping around the head." Often this discomfort may go up the scalp, through the neck, and down to the shoulders. The timeline for a tension headache tends to vary ranging from a half hour to chronic and continuous headaches lasting days to weeks.

After other primary and secondary causes of headaches have been considered, tension-type headaches are largely a diagnosis of exclusion. Although there may be some phonophobia or photophobia, those symptoms tend to be more commonly associated with migraine headaches. Although the specific etiology of the tension-type headache remains unknown, there are certain things that tend to trigger the headache, including stress, anxiety, dehydration, specific posture, sleep issues, and many others.

Cluster-Type Headaches

Cluster headaches are typically unilateral paroxysms characterized by a stabbing quality localized as being "right behind the eye." Occasionally, rhinorrhea or lacrimation accompanies cluster headaches. Subsequent episodes often develop a consistent laterality to the attack. Cluster headaches may have triggers that are patient dependent by tobacco use, alcohol use, or strong smells (typically due to work exposure, i.e., tarring, pesticide use, etc.) [14].

Usually these headaches occur in a group (or cluster) occurring every day for weeks at a time before they subside. Often when the headache episode resolves, patients may go for months or years before having another headache cluster. Treatment with oxygen is both therapeutic and diagnostic for this type of headache.

Medication Overuse Headaches (MOH)

The definition of a medication overuse headache contains two parts: a headache frequency coupled with medication overuse. These headaches are characterized by more than 14 headache days per month with regular overuse of >3 months with one or more treatment medications. Medication overuse is defined in two ways. The first definition is the use of a combination drug (such as aspirin with caffeine), ergot derivatives, opioids, and triptans for 10 or more days per month. The second definition is using acetaminophen, NSAIDs, or nonopioid analgesics for 15 or more days per month [7].

When physicians diagnose an MOH, in reality they are making two diagnoses: first a causative primary headache and then the resulting medication overuse [6]. Appropriate diagnosis and treatment of the underlying primary headache are the foundation for MOH prevention, and educating patient about the secondary etiology of the MOH may help. Through elimination of pain, the acute headache medication activates the reward pathways. As this pathway is activated and re-activated again, an MOH develops. This then sets up a feedback loop which amplifies primary headache pain [6] rendering the MOH difficult to treat.

Physical Examination

The focus on the physical exam is largely to rule out secondary causes of headaches. There are few specific physical exam findings specific to primary headaches. However, the family physician should undertake a thorough evaluation of the head and neck during the initial evaluation to determine the headache's type and then, as needed, if the headache changes or a new headache type presents. It is likely unnecessary to repeat a comprehensive head and neck examination with each stable subsequent follow-up visit.

The physician should first visually examine the head and neck for any gross abnormalities such as a herpetiform rash or other visual abnormality. Following this the cranium should be palpated with particular attention to the temporalis and

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paraspinal muscles. In tension-type headaches, these muscles may be tight and painful to the touch. The eyes should be inspected and assessed for light reactivity, photophobia, visual accommodation, and gross visual field deficits. The nares, mouth, and ears should be subjected to a lit otoscopic exam.

Of importance in examining headaches is the cranial nerve (CN) examination. CNs are special because they arise from the brain, and thus dysfunction greatly increases the likelihood of brain-specific pathology. Table 2 presents a structured approach to examining the cranial nerves [15].

Combining a careful history without red flags and an unremarkable physical exam, the physician will have ruled out a large number of secondary causes.

Laboratory and Imaging

Only if red flags are present, should the physician consider ordering laboratory tests. As in most other illnesses, laboratory evaluation should be tailored to the specific diagnostic considerations. For example, if the physician suspects giant cell arteritis due to funduscopic exam findings coupled with jaw claudication (the patient's complaint of "headache") or scalp tenderness, they should order an erythrocyte sedimentation rate. In diagnosing primary and medication overuse headaches, laboratory evaluation is usually unhelpful.

Absent red flags, medical literature and current guidelines recommend limiting neuroimaging. The Choosing Wisely campaign targets wasteful and ineffective medical practices by admonishing "Don't perform neuroimaging studies in patients with stable headaches that meet criteria for migraine" [16]. Imaging should be considered if red flags are present on initial evaluation or develop over time. Routine neuroimaging when diagnosing primary headaches to rule out pathology is wasteful and non-patient centered and should be discouraged.

Treatment

General Approach

While some headaches may be initially treated similarly with general analgesics, like NSAIDs, treatment imprecision may be costly and

Table 2 Cranial nerve exam components [15]

CN number	CN name	Exam technique
I	Olfactory nerve	Occlude each nostril, wave an EtOH swab or chlorhexidine swab under the open nostril, and ask if it can be smelled
II	Optic nerve	Visual acuity (with glasses worn), fields, and funduscopic exam
III	Oculomotor, trochlear, abducens	Bilateral equal pupillary response to light and object accommodation; with fixed head, patient's eyes following an H or star pattern drawn by examiner's fingers
IV		
VI		
V	Trigeminal	Light touch (fingertips) of the bilateral (V1), malar (V2), and skin lateral to chin (V3) of the face; patient should report equal sensation
VII	Facial	Upper component: patient tightly closes eyes, while physician assesses for equal strength
		Lower component: patient puffs out cheeks
VIII	Vestibulocochlear nerve	Whisper test in each ear
IX	Glossopharyngeal	Assess gag reflex or uvular deviation with patient saying "Ah"
X	Vagus	
XI	Spinal accessory nerve	Patient shrugs bilateral shoulders, while physician applies downward resistance
XII	Hypoglossal nerve	Symmetric tongue protrusion

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ineffective and create medication overuse headaches. Therefore, developing a sustainable individualized treatment strategy is critical to avoid harming the patient. The prevalence of iatrogenic medication overuse headaches demonstrates this principle clearly.

Behavioral Approaches

Sleep, diet, and exercise all interact with primary headaches. By capturing these relationships in a headache diary, the patient can meaningfully contribute to the development of a comprehensive treatment plan (see Fig. 2). Incorporating this information helps the physician attain greater success than exclusively focusing on pharmaceutical management.

There is a growing consensus that sleep and headaches are interrelated, and research suggests, in at least migraines, poor quantity of sleep is associated with more severe attacks [17]. Thus, it may be useful to obtain sleep-related history and screen for common sleep disorders such as obstructive sleep apnea which have been known to precipitate headaches.

The relationship between aerobic exercise and primary headaches is complex. Several large population-based studies suggest a link between low levels of exercise and increased frequency between migraine and other headache disorders. Migraines are known to be worsened by physical exercise, but routine exercise notably reduces frequency and intensity [18].

It is well known that diet impacts headache. Just as triggers are highly individualized, any dietary treatment approach should be patient specific. Identified food triggers for headaches include aged cheese, alcohol, aspartame, caffeine, chocolate, monosodium glutamate, nitrate, food preservatives, and red wine [19]. While fasting has been demonstrated as a trigger for some patients with migraine, it has been shown in others to decrease migraine frequency and intensity. Emerging evidence suggests effective headache prophylactic strategies may include reducing omega-6, increasing omega-3 fatty acids, weight loss diets in obese patients, low calorie, and ketogenic diets [20].

Medication Strategies for Migraine, Tension, Cluster, and Medication Overuse Headaches

Migraine Treatment

The primary goals of migraine treatment are reduction of migraine frequency, function restoration, and pain alleviation [21]. The two main treatments of migraine headaches are nonspecific general analgesics (i.e., NSAIDS) and migraine-specific treatments such as triptans and ergotamine derivatives. The physician may attempt a stratified approach where mild to moderate headaches are treated with NSAIDs and moderate to severe migraines treated with triptans or ergotamine derivatives [22]. Another approach, known as abortive treatment, involves initiating triptans at the earliest onset of an aura or the start of a migraine. In head to head trials, triptans and NSAIDs are noted to have similar efficacy, but triptans are useful any time during a migraine [23].

A 2016 meta-analysis suggested that the best migraine medication treatments within each class were ibuprofen (due to tolerability) and eletriptan (due to comprehensive efficacy). Additionally, diclofenac and the combination sumatriptan/naproxen were notable for their combination of efficacy and tolerability [23]. However, despite the possible superiority of eletriptan, selecting a triptan rests on clinician-patient preference for efficacy, costs, and tolerability [23] as eletriptan costs approximately three times more than sumatriptan [24].

While comprehensive mastery of the numerous NSAIDs and triptans is impractical, understanding a few examples of the NSAID and triptan classes typically suffices for treatment success (see Table 3). As with all prescribing, it is important to note specific contraindications. For example, NSAIDs as a class carry a risk of myocardial infarction, stroke, gut bleeding, and renal injury; triptans are contraindicated for peripheral vascular disease, ischemic bowel disease, ischemic heart disease, cerebrovascular vascular disease, basilar/hemiplegic migraines, uncontrolled hypertension, arrhythmias associated with a cardiac accessory pathway such as Wolff-Parkinson-White, or severe hepatic impairment.

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Finally, there are other medications which may be useful in select circumstances for severely debilitating migraine attacks. These medications include the non-migraine-specific opiates and migraine-specific ergotamine derivatives. Opioid medications can relieve head pain; however, this risk must be weighed against the risk of dependence and associated development of chronic headache, such as MOH [27]. The risk of rebound headaches in ergotamine derivatives diminishes their continued utility for acute migraine treatment when better alternatives are available [25], thus rendering both of these medications ill-suited for routine migraine relief.

Preventive therapy has been shown to decrease migraine, severity, and associated disability [28]. Migraine prevention should be considered if there is significant disability caused by migraines, greater than 4 migraine headache days per month, contraindications/adverse reactions to common acute migraine treatments, or patient preference [29]. Based on large population studies, although one in three patients with episodic migraines would benefit from preventive therapy, less than half of these patients are currently taking migraine prophylaxis [28]. Thus, family physicians can greatly enhance a patient's quality of life through prevention.

Once the physician and patient agree on a prevention strategy, it is helpful to discuss goals. Goals for preventive therapy include [30]:

1. 50% reduction in attack frequency with a decreased attack intensity and duration
2. Improve acute therapy efficacy
3. Improve patient function and decreased disability
4. Prevent MOH and chronic daily headache

These goals allow the clinician to define success for any prophylactic approaches. Prior to any consideration of pharmaceutical prophylaxis, nonpharmacologic prevention strategies should be considered, such as behavioral interventions along with complementary and alternative treatments which will be discussed later in the chapter.

The basic approach when selecting a preventive medication treatment begins with starting at a low dose and titrating slowly up to a therapeutic regimen while allowing time for an adequate trial and maximizing adherence [29]. The best documented evidence for migraine preventive treatments includes select beta blockers, amitriptyline, divalproex and topiramate [31]. Because these medications are usually taken daily, careful attention must be paid to the adverse effects and the possibility of polypharmacy, particularly in older patients. In particular, females of childbearing age should have a full discussion about the risk of teratogenicity of valproic acid and other pregnancy considerations. Despite the risk of polypharmacy, an elegant approach to the patient may consist of using one medication such as propranolol to treat two different conditions, say migraine prophylaxis and concomitant hypertension.

Additionally, it is important to note the availability of onabotulinum toxin A (Botox) as a migraine prevention treatment. This approach may prove useful in select cases; however, insurance coverage varies widely. Family medicine physicians should also be aware of the emerging classes of subcutaneous and injectable prophylactic medications, specifically the calcitonin-related gene peptide inhibitors. However, their current cost renders them most appropriate for referral centers and specialists. Because of the prevalence and disability associated with headaches, the opportunities for pharmaceutical innovation are endless, and likely there will be numerous niche additions to the pharmacopeia in the coming years.

Tension-Type Headache (TTH) Treatment

The first-line acute treatment for TTH tends to be behavioral and complementary and alternative medicine (CAM) treatments given their favorable risk profile [32]. However, given that TTH lack clear definable characteristics, care should be taken to ensure that competing diagnoses are reasonably excluded before designing a sustainable treatment regimen. The first line for pharmaceutical treatment is with NSAIDS for the acute headache (see Table 3 for additional information) [33]. Often, given the name, clinicians associate TTH with muscle tension and thus prescribe muscle relaxers for acute treatment. However, there

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Table 3 Acute headache treatments [16, 23–26]

Drug name	Usual dosage	Notes
Acetaminophen	MH, CH, TTH: oral, 325–1000 mg; max dose 4000 mg/day	Routine use may increase risk of hepatotoxicity
Aspirin	MH, CH, TTH: 325–600 mg oral once	Negatively against with MOH
Ibuprofen	MH, CH, TTH: 800 mg by mouth up to three times per day	Negatively associated with MOH
		Correlated with better tolerability
Ketorolac	MH, CH, TTH: 20 mg by mouth followed by 10 mg every 4 to 6 h to a maximum of 40 mg per day	Perhaps more efficacious than other NSAIDs
Naproxen	MH, CH, TTH: 750 mg by mouth initially then 250–500 mg as needed up to a maximum of 1250 mg in 24 h	Combination with sumatriptan improves tolerability of sumatriptan
Sumatriptan (generic available, branded as Imitrex)	MH, CH: oral, 50–100 mg daily, the repeat the dose after 2 h as needed up. Max dose is 200 mg daily	Available forms useful if nausea prevents oral route
	MH, CH: intranasal, 20 mg once in a single nostril; if partially effective repeat dose; max dose is 40 mg/day	Often, mild migraines are mistaken for TTH, so triptans may help with symptoms in this case
	MH, CH: subQ, 6 mg once if partially effective, repeat after 1 h with a range of 1–6 mg dose; max dose is 12 mg in 24 h	Least expensive triptan (Good Rx reference)
		Combination with naproxen improves tolerability
Rizatriptan (Maxalt)	MH: oral, 5 to 10 mg, repeat after 2 h if needed; max dose is 30 mg/day	Available as an oral disintegrating tablet
Eletriptan (Relpax)	MH:– oral, 20–40 mg as a single dose, repeat after 2 h if needed; max dose is	Not available in a non-tablet form which may limit utility in nausea
		Perhaps most efficacious
		Most costly
Zolmitriptan (Zomig)	MH, CH (off label): intanasal 2.5–5 mg once	
	MH, CH (off label): PO, 1.25–2.5 mg (CH can start with 5 mg once)	
Ergotamine	MH, CH (off label): sublingual 2 mg at first sign of headache (migraine, off label for cluster), then 2 mg q30 min, max dose 6 mg/day	Contraindicated within 24 h of triptan use
Oxygen therapy	CH: 100% oxygen at 12 L/min via non-rebreather mask	First-line treatment for CH
Caffeine	MH, TTH: typical caffeine dose 130 mg	Combination with ASA, acetaminophen, or both

For treatment of all headache types, routine opioid use is not recommended [16]
MH migraine headaches, *CH* cluster headaches, *TTH* tension-type headaches

have been no good trials to prove their efficacy, and given the safety profile, they are not recommended for inclusion in a TTH treatment regimen.

In addition to acute treatments, behavioral and complementary therapies remain the first-line treatment options for prevention [32]. However, specific literature to support this prevention strategy is limited. In terms of prophylactic pharmaceutical options, tricyclic antidepressants have been utilized for decades [34]. Other prophylactic medications to consider include mirtazapine and venlafaxine, but these medications are typically reserved to simultaneously treat a secondary diagnosis, i.e., depression (see Table 4 for full details).

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Cluster Headache Treatment

Given the low risk of oxygen therapy, and the aiding with diagnosis of cluster headache, it is often used as a first-line treatment. 100% O_2 is typically given at a high rate (usually 12 L/min) through a non-rebreather mask. Up to 70% of patients experience relief with oxygen therapy [14]. If the oxygen therapy doesn't alleviate the headache, often subcutaneous sumatriptan is the most appropriate choice for treatment. The brevity of cluster headache attacks renders the parenteral or nasal route most appropriate for therapy. A more thorough treatment outline can be found in Table 3. For prevention, after behavioral therapy and/or CAM trial, the pharmacotherapy of choice is verapamil. Other options may include topiramate and lithium which require close monitoring of serum levels [14]. Family medicine physicians should be aware that there exist surgical nerve destruction and neurostimulation as treatment options for cluster headaches. However, these modalities have conflicting results and thus are not routinely recommended at this time.

Medication Overuse Headache (MOH) Treatment

The three mainstays of MOH treatment are patient education, detoxification/withdrawal, and prophylactic treatments [35]. Patient education centers on discussing expectations and the rationale to reduce acute treatment medication. The primary headache and concomitant MOH attacks may increase in the short term, but over the long term, the patient's overall functioning and pain level should decrease. Similar to chronic pain, finding ways to disrupt the headache cycle, like withdrawal of the offending medication, either in an abrupt or tapered manner as appropriate will help reduce recurrent episodes. If the medication taken is an opiate, abrupt withdrawal is problematic and likely best managed in an inpatient setting. However, if the offending medication is acetaminophen, then outpatient management may be more suitable. There is minimal evidence to support one MOH medication over another. In patients with chronic migraine (as the primary headache) and MOH, topiramate in doses up to 200 mg/day has moderate evidence of efficacy [35].

Table 4 Suggestions for headache prevention medications [26, 30, 31]

Drug name (all oral)	Indication and suggested dosing	Pregnancy risks
Timolol	MH: 10 mg oral twice daily titrate to 30 mg oral twice daily	C: Decreased fetal heart rate, potential postdelivery bradycardia, hypoglycemia, and respiratory depression
Propranolol	MH: 40–240 mg PO daily	Not defined; bradycardia, hypoglycemia, and respiratory depression
Divalproex	MH: 500 mg once daily to 1000 mg daily	X: Neural tube defects, decreased child IQ after birth
Topiramate	MH, CH (off label): 25 mg once daily titrated to 50 mg twice a day over 4 weeks	D: Cleft palate, small for gestational age
Amitriptyline	MH (off label), TTH (off label): 10–25 mg/day at bedtime titrate up to 100–300 mg/day	C: Case reports of limb deformities, development delay; neonatal irritability and jitteriness
Verapamil	MH (off label), CH (off label): start at 40 mg TID IR or 120 XR daily, can titrate to 120 mg TID IR or 180 mg BID XR	C: Newborns exposed to this Rx should be monitored for fetal hypoxia

Note: In 2015, the FDA moved away from pregnancy risk categorization in favor of a more nuanced discussion of risk specifics; however, as these risk categories may assist the family physician in discussing relative risk, they have been included

MH migraine headaches, *CH* cluster headaches, *TTH* tension-type headaches

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Complementary and Alternative Medicine (CAM)

There is a growing body of literature exploring the use of complementary and alternative medicine therapies in headaches. However, the term CAM is imprecise, covering a broad range of therapeutic techniques. Examples of this include musculoskeletal manipulation (chiropractic care, massage, etc.), herbal supplements, and alternative medical systems (acupuncture, ayurveda, homeopathy, etc.) [36]. Another treatment patients may use includes "mind-body" therapy (such as yoga, meditation, deep breathing, tai chi, etc.), which notably many patients don't often disclose during the clinical encounter as a treatment modality they are using.

The overall quality of research evaluating musculoskeletal treatment research for headaches tends to be difficult to appropriately interpret given sample size and data source. Overall there seems to be conflicting evidence with some finding that based on intent-to-treat analysis, there is no significant difference between manipulated and controlled groups (specifically when looking at tension-type headaches) [37].

However, there is some evidence that suggests that chiropractic care may improve migraines and cervicogenic headaches [38]. In the end, given that this is typically an out-of-pocket cost for patients, like all things, it becomes an individualized conversation about the theoretical benefits versus the cost of such treatments.

The line of CAM that has the most significant research behind its use is acupuncture. Acupuncture has been utilized in many functions to help alleviate various types of headaches. Current research seems to indicate that typically it can reduce the number of days with headache in a given period of time for both tension-type headaches and migraines but that there is not a significant difference between true acupuncture and sham treatments [32, 39].

This leads to the impression either that there is a deeper etiology for the headaches, such that placebo treatment has a significant role in the resolution of discomfort, or that treatments like sham acupuncture can cause inflammation that in itself helps with symptomatic resolution even though they do not go along the lines of traditional meridian treatment.

Conclusion

Headaches have plagued humanity since the dawn of medicine. Still, physicians have grown increasingly adept at accurately classifying and diagnosing this common illness. But only in the past century, have medical researchers developed safe effective treatments from ergotamine derivatives of the 1920s to the triptan class of the 1990s and even beyond. Armed with knowledge of proper diagnosis and treatment, the family physician is well equipped to alleviate great suffering. Looking forward to the future, the treatment success with both sham and real acupuncture demonstrates that much work remains to be done to better understand and treat this common scourge.

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Epilepsy

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Epilepsy is a chronic neurological disorder characterized by recurrent seizures. A seizure happens when abnormal electrical activity in the brain causes an involuntary change in body movement or function, sensation, awareness, or behavior. Epilepsy is a chronic seizure disorder.

Epilepsy affects 2.3 million adults [1, 2], and more than 450,000 children 0 to 17 years old [2] in the United States. About 1 in 26 people will be diagnosed with epilepsy at some point in their lives [3].Epilepsy each year accounts for $15.5 billion in direct costs (medical) and indirect costs (lost or reduced earnings and productivity). More than one-third of people with epilepsy continue to have seizures despite treatment. Each year, about 200,000 new cases of epilepsy are diagnosed in the United States.

The International League Against Epilepsy redefined Epilepsy in 2014 [4]. Epilepsy is defined as (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome.

Epilepsy is considered resolved for individuals who either had an age dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last 10 years and off anti-seizure medicines for at least the last 5 years. Indicating that epilepsy is no longer considered to be a lifelong disorder.

Types of Seizures and Epilepsy

The two main types of seizures are Generalized and Focal. In Generalized seizures there is involvement of both cerebral hemispheres. And in focal seizures the seizure involves one hemisphere or a lobe of a hemisphere. The vast majority of seizures are Focal seizures, between 70–80% in adults (Fig. 1).

Generalized Seizures

Generalized Seizures are conceptualized as rapidly engaging bilaterally distributed networks involving both hemispheres. Such bilateral networks can include cortical and subcortical structures. On scalp EEG they seem to be present all over and hence the use of the word generalized.

Generalized seizures are further subdivided into tonic-clonic (which is used to describe

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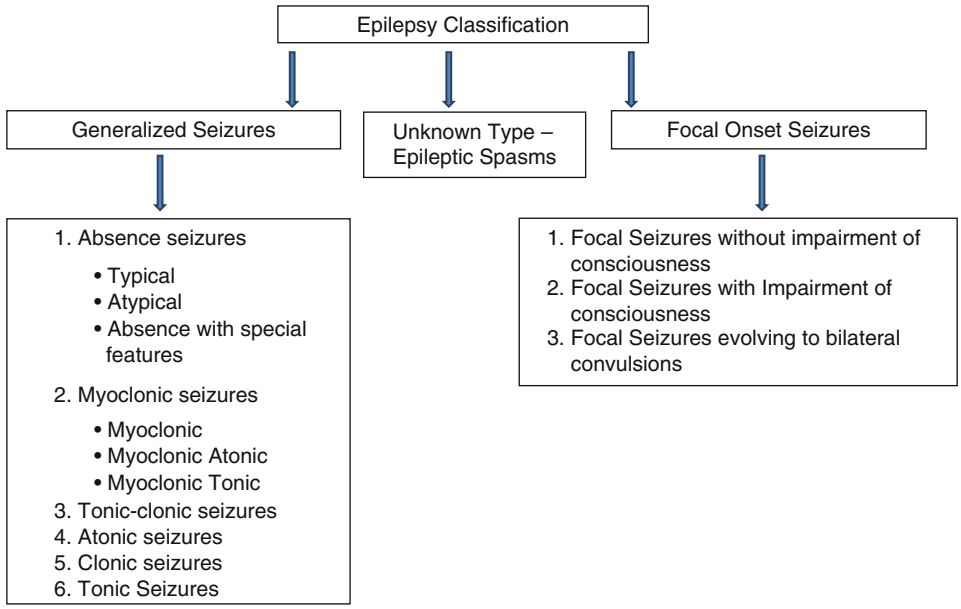


Fig. 1 Epilepsy classifications

stiffening of all four extremities in the tonic phase and rhythmic shaking all extremities in the clonic phase). This was referred to as "Grand Mal." In absence seizures, the basic phenomenon is a blank stare, absence seizures can be typical, atypical or have special features. Other kinds of generalized seizures are myoclonic seizures, clonic seizures, tonic seizure, and atonic seizures (also known as drop attacks).

Focal Epileptic seizures are conceptualized as originating within networks limited to one hemisphere or even one lobe. They may be discretely localized or more widely distributed. The focal seizures can be with or without impairment of consciousness and may secondarily generalize.

Clinical Manifestations

Epileptic seizure can have variable clinical manifestations including many types of auras. After each seizure, there might be a post ictal period, the length of which is variable. The first step in diagnosing epilepsy is obtaining a detailed description of the Aura(warning before a seizure), Ictus (the actual seizure), and Post-ictal phase (immediately after a seizure) from the patient and an observer.

Generalized Seizures

Generalized seizures are thought to arise at some point within the brain and rapidly involved both hemispheres. Different types of generalized seizures have distinct clinical and electrographic features.

Absence Seizures

Typical Absence Seizure

Absence epilepsy accounts for 10–17% of all cases of childhood onset epilepsy, making it the most common form of pediatric epilepsy. The syndrome is characterized by daily frequent brief staring spells, typically beginning at 4–8 years of age, in an otherwise apparently healthy child. The classic electroencephalogram (EEG) displays 3 Hz generalized spike-wave bursts.

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Majority of the seizures last between 5 and 20 sec. Seizure onset is sudden and the child becomes motionless with a vacant stare. The eyes may drift upwards and there is slight beating of the eyelids. Typical absence seizures are frequently repeated many times per day with reports to as many as 100 or more times per day.

Hyperventilation (for about 2 mins) tends to provoke these seizures and can be used in a clinic setting as a diagnostic tool but with caution.

Atypical Absence Seizures

Atypical absence seizures have less abrupt onset and offset, more pronounced changes in tone, variable impairments of consciousness, and tend to last longer than typical absences. They are most likely to occur during drowsiness and are not provoked by hyperventilation or photic stimulation .

Other types of Absence seizures include Myoclonic Absence Seizures & Eyelid Myoclonia with Absence seizures.

Generalized Tonic-Clonic (GTC) Seizures

These seizures usually begin with stiffening of muscles in all extremities along with axial and laryngeal muscles which leads to a loud moan also refer to as an "ictal cry." This is referred to as a tonic phase off the seizure. Following this there can be rhythmic jerking of the arms and legs which is referred to as the clonic phase. An aura is usually not present prior to the seizures.

During the seizure there can be tongue bite and/or urinary and fecal incontinence. During the tonic phase the patient is not breathing, and in children it can lead to perioral cyanosis. Rarely during the tonic phase, one can fracture the vertebral bodies and so back pain after a seizure should be carefully evaluated.

When the patient is having a generalized tonic-clonic seizure the area around him or her should be cleared of any sharp or dangerous objects that might cause injury to the patient if they were to bump into the objects. No attempt should be made to insert any foreign objects in to the patient's mouth. And while the patient is in the clonic phase, no attempt should be made to forcibly hold him down as this can lead to injury.

Myoclonic Seizures

Myoclonus is a brief sudden and involuntary contraction of one part of the body or muscle group. This could either be epileptic or non-epileptic. Myoclonus can occur physiologically when patients are falling to sleep. Myoclonic seizures are characterized by brief, sudden, involuntary muscle contractures involving different combination of head, trunk, and limbs. On EEG, the generalized spike wave or poly-spike and wave discharges are noted with these myoclonic jerks.

The commonest type of Myoclonic Epilepsy is Juvenile Myoclonic Epilepsy (JME). This type of epilepsy starts in the teenage years; it is obviously characterized by Myoclonic, but in about 80% of cases they also have GTC seizures. Rarely, they can also have absence seizures.

Atonic Seizures

Atonic seizures are characterized by a brief and sudden loss of postural muscle tone which usually results in frequent falls (Drop Attacks) in these patients. These last a few seconds and usually do not have any post-ictal confusion.

Focal Seizures

In the past, Focal seizures were referred to as Partial seizures. These were characterized as simple partial and complex partial seizures based on loss of consciousness. However, using the term simple and complex was misleading to the patient who could easily misinterpret these connotations as simple being easier to treat or have a better prognosis as compared to complex seizures. Hence the term focal is more appropriate in the new classification.

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Focal Seizures without Impairment of Consciousness

Focal seizures can present as motor, sensory or autonomic seizures. These mostly.

arise in patients with a structural brain abnormality. For example, a person with a brain tumor in the motor cortex can have rhythmic shaking of his contralateral arm without impairment in consciousness. These can be rather challenging to treat in certain cases and refractory to medications. In the past, these were known as simple partial seizures.

Focal Seizures with Impairment of Consciousness

These were previously referred to as complex partial seizures. They usually consist off an aura which is specific and stereotypical. The patient will have a sudden behavioral arrest along with automatic as well as in certain cases. Automatisms consist off lip smacking, picking hand movements, swallowing, and chewing. Automatisms are ipsilateral to seizure onset region and can be helpful in lateralizing seizure onset to right or left hemisphere.

Focal Seizures Evolving to Bilateral Convulsive Seizures

These were previously referred to as complex partial seizures with secondary generalization. This term has been now replaced with bilateral convulsive seizures. These usually consist of an aura and electrographically the seizure discharge spreads to both hemispheres including the motor strip which causes tonic-clonic seizures. These patients tend to have an aura which makes it different from generalized seizures where it might not be present. Also, paying attention to automatism and forced head deviation can help with lateralization and localization.

Focal seizures are usually referred to by the lobe of the cortex the seizures originate in (Table 1).

Seizure Syndromes by Age Group

Neonatal Period

- Benign familial neonatal epilepsy (BFNE).
- Early myoclonic epilepsy (EME).
- Ohtahara syndrome.

Infancy

- Dravet syndrome.
- West syndrome.
- Epilepsy of infancy with migrating focal seizures.
- Benign infantile epilepsy.
- Myoclonic epilepsy of Infancy.
- Myoclonic encephalopathy in non-progressive disorders.
- Benign familial infantile epilepsy.

Childhood

- Febrile seizures plus.
- Panayiotopoulos syndrome.
- Benign epilepsy with centro-temporal spikes (BECTS).

Table 1 Focal seizures clinical characteristics

Focal seizures	Clinical characteristics
Temporal lobe seizures	Aura – Epigastric sensation, déjà vu, abnormal taste or smell, intense anxiety Ictus – Blank stare, with or without oral automatisms, hand automatisms Post-ictal – Confusion & disorientation
Frontal lobe seizures	Usually motor seizures, vocalization (dominant hemispheres) nocturnal seizures, brief in duration, fencing posture, bicycling leg movements, Jacksonian march, forced eye/head deviation, may have no postictal period.
Parietal lobe seizures	Paraesthesias
Occipital lobe seizures	Visual phenomenon

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- Epilepsy with myoclonic atonic seizures.
- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).
- Gastaut syndrome.
- Epilepsy with myoclonic absence.
- Lennox-Gastaut syndrome.
- Landau-Kleffner syndrome.
- Childhood absence epilepsy.
- Epileptic encephalopathy with continuous spike and wave during sleep.

Adolescence

- Juvenile absence epilepsy.
- Juvenile myoclonic epilepsy.
- Progressive myoclonic epilepsies.
- Epilepsy with generalized tonic-clonic seizures alone.
- Autosomal dominant epilepsy with auditory features.
- Other familial temporal lobe epilepsies.

Less Age Specific

- Reflexive epilepsies.
- Familial focal epilepsy with variable foci.

Seizures in Neonates and Infants

Benign Familial Neonatal Seizures

These are also known as Third day fits. Seizures consist of tonic stiffening, apnea/cyanosis, autonomic signs, face and limb clonus, lasting about 1–3 min. These are associated with a potassium channel abnormality in the KCNQ2 & 3 channels. Seizures usually last for about 3–6 months and then resolve spontaneously.

Early Infantile Epileptic Encephalopathy (Ohtahara)

Ohtahara syndrome affects newborns, usually within the first 3 months of life (most often within the first 10 days) in the form of epileptic seizures. More common in males. Infants have primarily tonic seizures, but may also experience partial seizures, and, rarely, myoclonic seizures. Ohtahara syndrome is usually caused by metabolic disorders or structural damage in the brain, although the cause or causes for many cases can't be determined. Majority of the cases have cortical malformation. The EEG of infants with Ohtahara syndrome reveal a characteristic pattern of "burst suppression." Usually drug resistant epilepsy.

Early Myoclonic Encephalopathy

These occur typically within the first one month of life. As the name describes myoclonic seizures are the predominant type in this syndrome. Patients usually have a concurrent nonketotic hyperglycinemia. There is progression to tonic spasms as they grow older.

Infantile Spasms

These can be extensor or flexor spasms and typically occur between 4 and 8 months of life. Also known as "salaam attacks" in the past. It tends to occur in clusters and tend to be at the time of sleep wake transition. There is sudden flexion or extension of all extremities including the axial musculature which corresponds to an electrodecremental response on EEG. EEG background is high voltage slowing, disorganized pattern with multifocal sharps also referred to as hypsarrhythmia. Most patients have intellectual disability. Treatment includes ACTH and Vigabatrin.

Benign Myoclonic Epilepsy of Infancy

Onset is usually between 4 months and 3 years of age and patients eventually outgrow this. There is sudden jerking of the extremities along with eyedrops which make him look like infantile spasms. The EEG, however, shows a generalized spike and polyspike pattern instead of the classical hypsarrhythmia seen in infantile spasms . Also

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they have a normal development which clearly distinguishes this from infantile spasms. The main treatment is valproate; other options include levetiracetam or clonazepam.

Seizures in Childhood

Febrile Seizures

These occur between 6 months and 5 years of age. Febrile seizures are convulsions brought on by a fever in infants or small children. During a febrile seizure, a child often loses consciousness and shakes, moving limbs on both sides of the body. There are simple and complex febrile seizures.

Simple Febrile Seizure

Around 80–90% of all febrile seizures are simple febrile seizures. The setting is fever in a child aged 6 months to 5 years. The single seizure is generalized and lasts less than 15 min. The child is neurologically normal. The cause of the fever is always outside the central nervous system. No antiepileptic medications needed.

Complex Febrile Seizures

The seizure duration is greater than 15 min. There are focal seizure manifestations or there is seizure recurrence within 24 h. Abnormal neurological status of the child and a family history of epilepsy. These seizure have a worse prognosis and have a much higher incidence of subsequent epilepsy.

Occurs in about 3–5% of the US population with a median age of 18 months. About one third of these patients will have a second febrile seizure (23–42%). At about half of those, one third will have a third febrile seizure (7–30%). Higher recurrance when the age of onset is under 1 year.

Management of febrile seizures

1. Lumbar puncture to rule out infection as indicated clinically.
2. CBC, S. Calcium, S. Electrolytes, UA.
3. EEG.
4. MRI – If prolonged or focal febrile seizure or clinically indicated.

Dravet Syndrome or Severe Myoclonic Epilepsy of Infancy (SEMI)

Dravet syndrome appears during the first year of life often triggered by hyperthermia, it is usually a generalized tonic-clonic seizure or hemiclonic seizure. Later, other seizures types arise, including myoclonus. Status epilepticus may also occur. Children with Dravet syndrome typically experience poor development of language and motor skills. They are known to be hyperactive. There is a genetic cause identified – SCN1A mutation or copy number variant in 80% of cases. Usually pharmacoresistant. Medications acting via sodium channel can make seizures worse like carbamazepine, oxcarbazepine, etc. Treatment options are Valproate, Topamax, Stiripentol, and Cannabidiol.

Rolandic Epilepsy or Benign Epilepsy with Centro-Temporal Spikes (BECTS)

This is the most common focal epilepsy in childhood with onset between 2 and 13 years of age with a peak around 7–10 years of age. It is mostly bilateral although in some cases it can be unilateral. Seizures usually occur during the first part of the night but 10–20% of the patients can have daytime seizures as well. Seizures can be sensory or motor consisting of drooling as well as abnormal feeling in the tongue, lips, and gums, or abnormal movements of the tongue larynx and pharynx. Rarely they can generalize as well.

EEG shows centro-temporal spikes more during drowsiness and sleep. Carbamazepine and Valproate are useful as initial monotherapy. Treatment beyond the age of 14 to 16 years is not indicated as BECTS resolves by that age.

Lennox Gastaut Syndrome (LGS)

LGS is characterized by multiple seizure types, mental retardation and a diffuse slow spike and wave discharge on EEG [5]. LGS is characterized by the patient having multiple seizure types which include atonic, atypical absence, tonic, focal, as

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well as generalized tonic-clonic seizures. Seizure onset is around 3–5 years of age. LGS patients can have preceding infantile spasms. EEG shows a characteristic slow generalized spike and wave pattern with a frequency less than 2.5 Hz. Treatment options are topiramate, levetiracetam, lamotrigine, clobazam, rufinamide, and cannabidiol. Vagal Nerve Stimulation is also an option. Corpus Callosotomy and Ketogenic diets have also been used.

Landau Kleffner Syndrome

This presents with seizures along with progressive aphasia (apparent word deafness or verbal auditory agnosia) and language regression. The peak onset is around 3–6 years of age and is more common in boys. EEG shows continuous generalized spike and wave activity during sleep also known as ESES (Electrical status epilepticus of sleep). Typically they have seizures first and then there is onset of regression. Eventually, Seizures tends to resolve more than the regression. Sodium channel antiepileptic drugs (PHT,CBZ,OXC) should be avoided in these patients. Corticosteroid treatment has shown benefit in Landau Kleffner syndrome. Multiple subpial transection (MST) surgery has been used in selected cases, although of unproven benefit.

Seizures in Adolescence

Juvenile Myoclonic Epilepsy

This is the most common form of generalized epilepsy in the adolescent age group typically occurring between 12- and 8 years of age. Most of the seizures are upon awakening. They can have myoclonic seizures, absence seizures and generalized tonic-clonic seizures.

The children will have myoclonic jerks early in the morning. For example, sudden jerking of the hand while brushing her teeth or spilling milk while eating cereals. They can have generalized tonic-clonic seizures in 80% of the cases. These patients are very photosensitive and video games can often trigger seizures. EEG shows diffuse 4–6 Hz generalized spike/polyspike and wave pattern. A genetic locus for JME is in chromosome 6p11.

Sodium channel antiepileptic medications like carbamazepine should be avoided in these cases as they can make the seizures worse. Levetiracetam, Valproic acid, and lamotrigine are better choices for antiepileptic drug therapy. A large number of these patients are well controlled on antiepileptic medications which have to be continued throughout their life.

Management of Seizures

History

It is important to ask the *age of seizure onset* as this information helps in the diagnosis of the type of seizure, as explained in the preceding section. Next one should inquire about the *seizure risk factors* like perinatal hypoxia, family history of seizures, history of febrile seizures (can be associated with temporal lobe seizures), any head injury with loss of consciousness, and any history of meningitis or encephalitis. Next, it is important to get a description of the seizure from an eyewitness and the patient. The patient should be asked about any warning before the seizure – *Aura*. The eyewitness should be asked about the seizure itself – *Ictus* and then the *post-ictal phase.* Then we need to find out about the duration and frequency of the seizures. All of the above information is critical to making an accurate diagnosis. As Temporal Lobe seizures last for a minute whereas frontal lobe seizures can last for seconds, temporal lobe seizures usually occur a few times a week whereas frontal lobe seizures can occur a few times a day.

Next, we need to find out what antiepileptic drugs(AEDs) the patient is taking and also ask about the AEDs that the patient has used in the past. It is important to find out the results of the workup undertaken in the past like CT Head, MRI Brain, EEG, and Video-EEG.

Neurological Exam

A good neurological exam is of critical importance in patients being evaluated for seizures. It

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is important to note any external signs of trauma; a good cognitive exam is important to see if there are any associated cognitive deficits. Dysmorphic facial features should also be noted as they may be associated with cortical malformations. Head circumference should be measured. Dermatological stigmata can give clues to a neurocutaneous disorder. Deficits on motor, sensory exam can indicate a hemispheric lesion.

Neuroimaging

MRI Brain is the investigation of choice and should be done with and without Gadolinium. We are looking for obvious cortical lesions causing seizures like tumors, stroke, cortical malformation, etc. It should also be done to check for a very common abnormality seen in Temporal Lobe Epilepsy, Mesial Temporal Sclerosis (MTS). In MTS, there is unilateral atrophy of the hippocampus involved and there is an increase in the T-2 signal in that hippocampus. CT Head is done in the Emergency Department essentially to rule out a bleed or other obvious abnormalities.

Every seizure patient should get an MRI Brain and an EEG (Figs. 2 and 3).

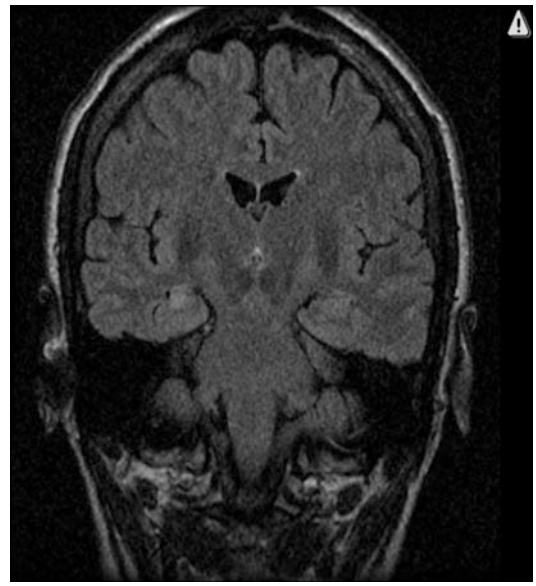


Fig. 2 MRI Brain Coronal FLAIR– Mesial Temporal Sclerosis – Increased T2 signal

Electroencephalography (EEG)

EEG is an essential test for all seizure patients. It helps in the diagnosis and classification of seizures. EEG is a graphical representation of the electrical activity of the brain as recorded by electrodes placed on the scalp of the patient (Fig. 4). It can show focal epileptic discharges suggestive of focal epilepsy or it can show generalized(diffuse) epileptiform discharges diagnostic of generalized epilepsy (Figs. 5 and 6). Spikes, sharps, polyspikes, and spike and wave discharges are the epileptic discharges indicating a tendency to have seizures.

A normal EEG does not rule out epilepsy as it is only abnormal in one third of the cases of definite epilepsy. Repeating the EEG does increase the yield in cases of epilepsy.

Video-EEG Monitoring

This is an inpatient testing in the Epilepsy Monitoring Unit of the hospital. The patient is hooked up to the EEG and is also being monitored simultaneously on video; they stay from one to a few days till the required data is gathered. Video-EEG monitoring is required in specific circumstances. It is an advanced testing done for epilepsy evaluation. It is performed when the physician needs to establish whether the paroxysmal spells represent epileptic seizures. It is also done to establish the type and frequency of seizures. And it represents the initial step in seizure focus localization for epilepsy surgery.

Other Tests

There are certain other tests done for epilepsy particularly for epilepsy surgery. These include FDG-PET Scan which determines the uptake of radiolabeled glucose by the brain. The epileptic focus is malfunctioning and so does not take up the glucose as well as the other regions. Neuropsychological Testing is done to determine the area of the brain that is not functioning optimally. The other tests done include a SPECT Scan (measures blood flow) and Magnetoencephalography.

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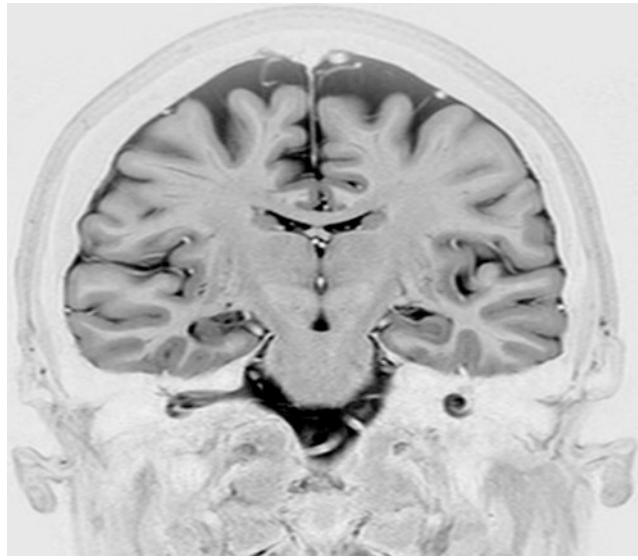


Fig. 3 MRI Brain Coronal view – Left MTS – hippocampal atrophy

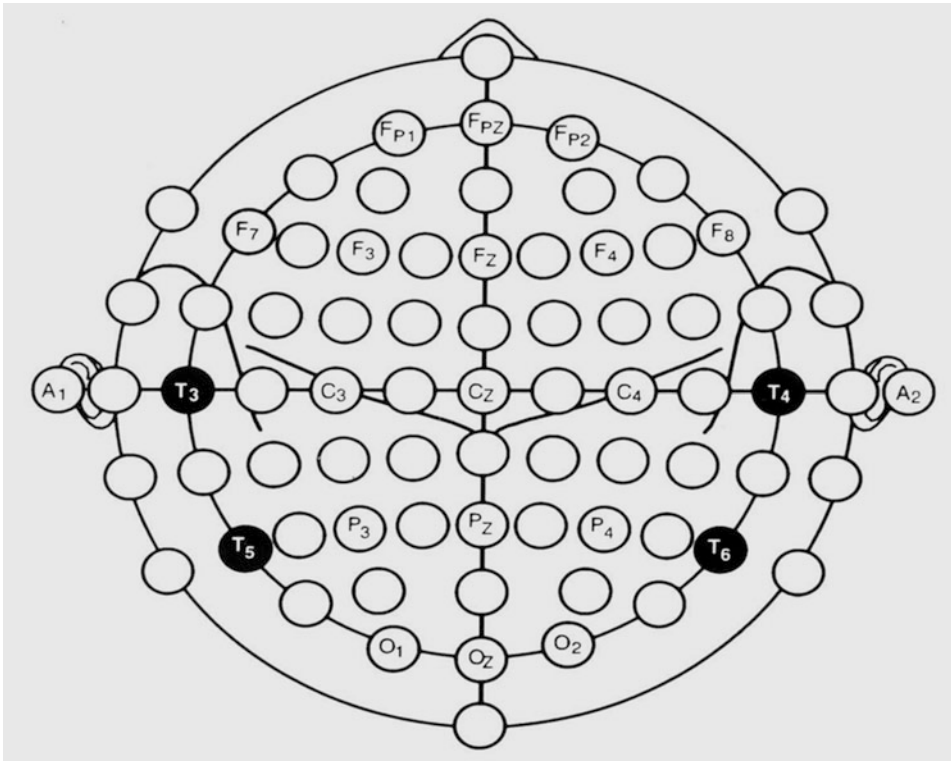


Fig. 4 EEG – Recording electrodes

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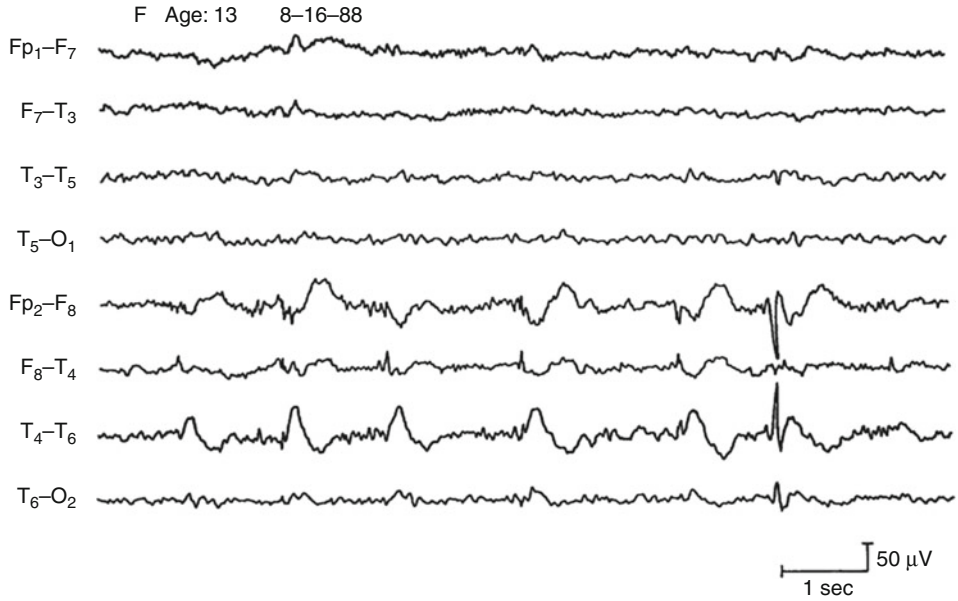


Fig. 5 Focal Epileptiform Discharge – Right Temporal Spike

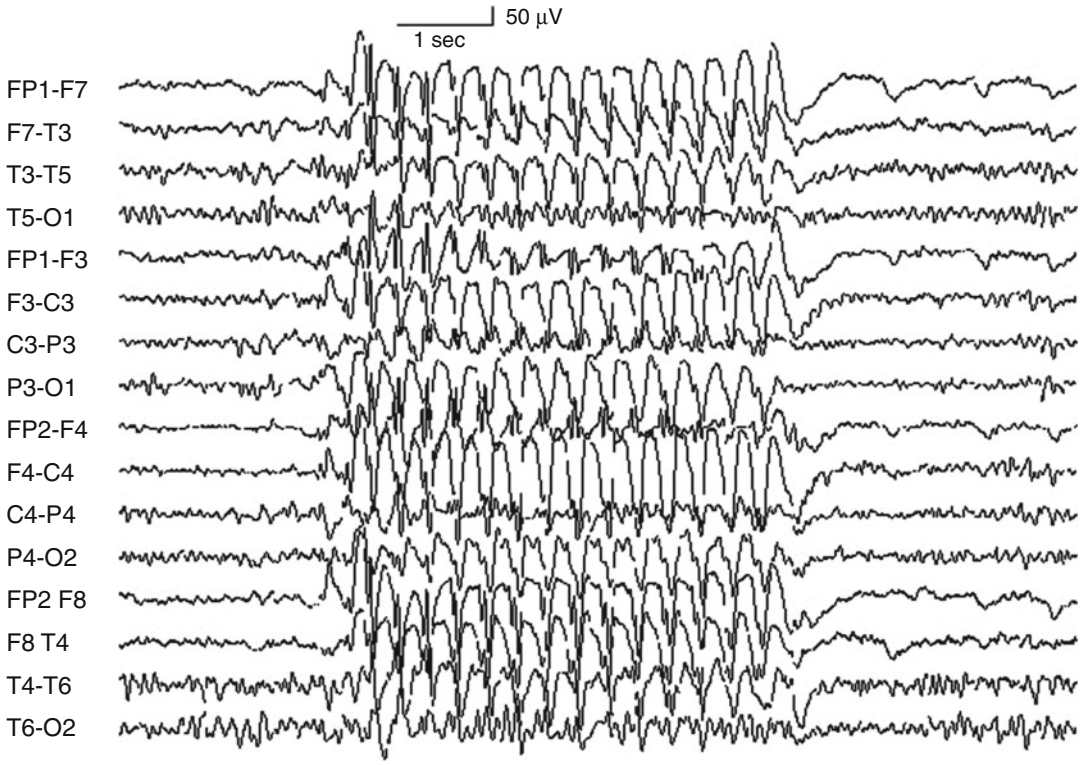


Fig. 6 Generalized epileptiform discharges – 3 Hz spike and wave discharge

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Medical Treatment

Medications are the mainstay for the treatment of epilepsy [6]. Approximately 70% of epilepsy patients can be treated by anti-epileptic drugs (AEDs). There has been an increase in the number of medications available for the treatment of epilepsy in the last two and a half decades (Table 2).

A good clinical pearl to follow when using all AEDs is "start low and go slow," start at a low dose and titrate up slowly based on clinical response. Drug Interactions are an important thing to keep in mind while using AEDs. Hormonal contraceptives can be compromised by the following antiepileptic medications – phenytoin, carbamazepine, phenobarb, Topamax, lamotrigine, and oxcarbazepine.

All AEDs may cause suicidal thoughts or actions in a very small number of people and one should educate the patients about this possibility and monitor them for this.

Carbamazepine may worsen seizures in Myoclonic epilepsy.

Epilepsy Surgery

When patients do not respond to medications then they are candidates for resective epilepsy surgery, this is a possibility if there is a localized seizure focus that can be safely resected. Epilepsy surgery is certainly recommended in refractory Mesial Temporal Lobe Epilepsy (MTLE), as a randomized study has shown that such patients who underwent surgery (Anterior Temporal Lobectomy) had a 58% seizure freedom rate as opposed to only a 8% seizure freedom rate for those treated with further medications. Resective epilepsy surgery may involve intracranial EEG recording.

Vagal Nerve Stimulation

Vagal nerve stimulation is an FDA approved form of treatment of refractory epilepsy. It is successful in about 40% of cases and success is defined as a 50% reduction in seizures. This device is surgically implanted, pulse generator in the chest and electrodes on the vagus nerve in the neck. The stimulation parameters can be managed externally by a programming wand and a computer via radiofrequency signals.

Deep Brain Stimulation (DBS)

DBS is another FDA approved treatment for people 18 years and older with medically refractory partial-onset epilepsy. DBS for epilepsy targets the anterior nucleus of the thalamus. There are two parts to the surgery, leads are placed bilaterally in the anterior nucleus of the thalamus and the neurostimulator is implanted under the skin in the upper chest. The responder rate (percentage of subjects with $\geq$50% seizure reduction) was 43% at one year and 74% at year seven.

Responsive Neural Stimulation (RNS)

This is another treatment option for medically refractory focal epilepsy. This is an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures.

Status Epilepticus

Status epilepticus is a life-threatening emergency requiring immediate medical attention and affects 65,000 to 150,000 people in the United States each year [9]. It is not a disease itself but rather a manifestation of either an underlying primary central nervous system insult or a systemic disorder with secondary effects.

Roughly 55,000 deaths are associated with status annually. There is about a 20% mortality in status epilepticus.

The definition of status epilepticus is having continuous seizure activity for greater than 30 min or 2 or more sequential seizures without

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Table 2 Antiepileptic medications - summary

Name of antiepileptic medication	Indication	Major side effects	Miscellaneous
Phenytoin	Focal epilepsy, secondary generalization, GTC seizures	Hepatic insufficiency, bone density decrease, rash, Ataxia, Hirsuitism	Monitor LFTs
Carbamazepine	Focal epilepsy, secondary generalization	Bone marrow depression, hyponatremia, liver insufficiency, rash, ataxia, bone density decrease	Monitor CBC, CMP,
Valproate	Generalized seizures, secondarily generalized seizures.	Hepatic failure, tremors, hair loss, weight gain, teratogenecity	Monitor LFTs
Phenobarb	Focal seizures	Sedation	Monitor cognitive decline
Oxcarbazepine	Focal seizures	Hyponatremia (more common in elderly), rash	Hyponatremia in the first 3 months
Lamotrigine	Focal seizures, generalized seizures	Rash, including Stevens Johnson and toxic epidermal necrolysis hypersensitivity reactions.	Side effects more common with concomitant valproate use and reduced with slow titration
Levetiracetam	Focal & generalized seizures	None	Irritability/behavior change
Topiramate	Focal & generalized seizures	Nephrolithiasis, open angle glaucoma, hypohidrosis in children	Metabolic acidosis, weight loss, language dysfunction
Zonisamide	Focal seizures	Rash, renal calculi, hypohidrosis in children	Irritability, photosensitivity, weight loss
Gabapentin	Focal seizures	None	Weight gain, peripheral edema, behavioral changes in children
Pregabalin	Focal seizures	None	Dizziness, somnolence, weight gain, edema, blurred vision, and peripheral edema
Ethosuximide	Generalized – Absence seizures	Allergic reaction-DRESS, pancytopenia, nausea, abdominal pain, rash	Used only for absence epilepsy
Eslicarbazepine	Focal seizures	Allergic reaction, rash	Dizziness, sleepiness, nausea, headache, double vision, vomiting, feeling tired, problems with coordination, blurred vision, hyponatremia and shakiness
Perampanel	Focal seizures & generalized seizures	Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported.	Dizziness, somnolence, fatigue, irritability, falls, nausea, ataxia, balance disorder, gait disturbance, vertigo and weight gain
Clobazam	In the USA, it is approved for use only as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome	Stevens-Johnson syndrome and toxic epidermal necrolysis	Constipation, somnolence or sedation, pyrexia, lethargy, and drooling

(continued)

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Table 2 (continued)

Name of antiepileptic medication	Indication	Major side effects	Miscellaneous
Rufinamide	As adjunctive treatment of seizures associated with Lennox-Gastaut syndrome	Multi-organ hypersensitivity, known to shorten the QT interval	Headache, dizziness, fatigue, somnolence, and nausea
Cannabidiol *(Marijuauna based)*	Lennox-Gastaut syndrome and Dravet syndrome	Hepatsic injury, omnolence, hypersenstivity reaction	Somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor-quality sleep
Cenobamate	Focal or partial-onset seizures	DRESS/multiorgan hypersensitivity – Particularly with fast titration, shortening of the QT interval	Somnolence, dizziness, fatigue, diplopia, and headaches

full recovery of consciousness to baseline. However, with the need for prompt care of patients, there is an operational definition that is used for management purposes, which is seizures lasting longer than 5 min are considered to be Status Epilepticus.

The initial management is like managing any medical emergency, airway, breathing, and circulation need to be attended to. Check for blood sugar, give 50% glucose and thiamine as indicated. Establish two I/V lines as you should avoid infusing Dilantin through an I/V that has been used to give glucose. Send labs including drug levels and a toxicological screen. Treat hyperthermia, but avoid treating high blood pressure unless there is end organ damage, as the blood pressure will come down as you treat status epilepticus.

The drug treatment of status epilepticus follows a protocol. Here we describe the Creighton Status Epileptics Treatment protocol [8] (Fig. 7). The drug of choice for initial treatment is Lorazepam [7]. Then the patient is given Phenytoin. After phenytoin, there are two options, one is to administer phenobarb and the other is to go to anesthetic agents directly. However, before any of these two options are exercised, the patient must be electively intubated as both these medications will suppress the respiratory drive. These patients must be on continuous EEG monitoring to determine whether the patient has stopped having seizures, as the patient maybe in nonconvulsive status epilepticus or after paralyzing the patient for intubation this is the only way we can find out about seizure activity.

The other drug options for initial treatment of status epilepticus are intramuscular midazolam or I/V diazepam. Other medications that can be used after the initial treatment are I/V Levetiracetam or I/V Valproic Acid.

Specific Conditions

Sudden, Unexplained Death in Epilepsy (SUDEP)

Sudden Unexpected Death in Epilepsy (SUDEP) is a nonaccidental death in a person with epilepsy, who was otherwise in a usual state of health. On autopsy, no other of cause of death can be found. The death should not be due to status epilepticus, which is a prolonged life-threatening seizure episode.

The rate of SUDEP is approximately one death per 1000 in people with epilepsy per year. In people with frequent epileptic seizures that are poorly controlled with medications, the rate is approximately 1 in 150 per year.

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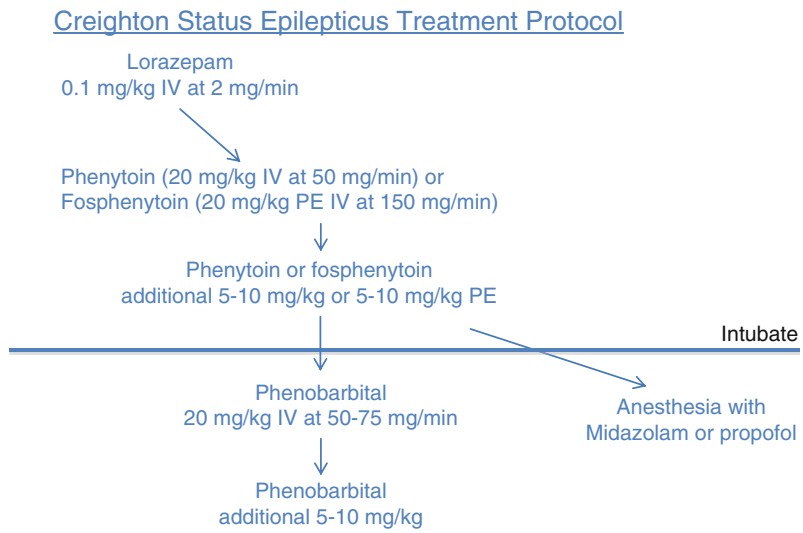


Fig. 7 Creighton status epilepticus treatment protocol

The risk factors for SUDEP include the following:

- Having uncontrolled generalized tonic-clonic seizures.
- Early age of epilepsy onset or long duration of epilepsy.
- Not taking medications as prescribed.
- Stopping or changing medications abruptly.
- Young adult age (20–40 years old).
- Intellectual disability (IQ $<$ 70).

Women with Epilepsy

There are important unique issues to consider when treating women with epilepsy. Estrogen is a proconvulsant and progesterone is an anticonvulsant [11]. During the menstrual cycle seizures can be exacerbated during midcycle, due to an estrogen peak, and then during menstruation due to progesterone withdrawal. Pregnancy in women with epilepsy causes worsening of seizures in one third of cases, no change in another third, and improvement of seizures in one third of patients. All antiepileptic medications can cause teratogenicity and so patients should be educated about this on the first clinic visit and they should be started on Folic Acid. Vaproate has the highest risk of teratogenicity and should be avoided in women in child-bearing age group. Breast feeding is recommended but the child's pediatrician or family physician should be aware of the antiepileptics the mother is on. Certain antiepileptic medications can result in failure of hormonal based oral contraceptives, like phenytoin, phenobarb, carbamazepine, and lamotrigine. Please check the prescribing information of AEDs to confirm the current teratogenic effects and its effect on hormonal contraceptives.

First Seizure

The risk of recurrence after a first seizure is about 33% without any testing. If both the MRI Brain, neurological exam, and EEG are within normal limits then the risk decreases to about 24% and thus we do not start such a patient on chronic antiepileptic medication. If both are abnormal as in the case of a cortical tumor, the risk of recurrence is high and so we do recommend treatment with an antiepileptic medication [10]. When a patient has a second seizure, then the risk of the third seizure is over 70% and so we then do recommend treatment with antiepileptic medications. And thus, the definition of epilepsy is two or more unprovoked seizures.

First Seizure Management

1. History.
2. Physical examination.

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3. Labs – Complete blood counts, Complete metabolic panel and urine drug screen.
4. Rule out mimics.

- Syncope.
- Hyperventilation.
- Panic attack.
- Psychogenic seizure.
- Transient ischemic attack.
- Transient global amnesia.
- Migraine equivalents.

5. Imaging – MRI brain with and without contrast (Preferable) or CT head with and without contrast.
6. EEG – Higher yield with sleep deprived EEG.

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Cerebrovascular Disease

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Kamal C. Wagle and Cristina S. Ivan

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General Principles

Introduction

Cerebrovascular disease (CVD) is a general term encompassing the brain abnormalities that result from pathologies of its blood vessels (e.g., atherosclerotic stenosis, aneurysm, dissection, inflammation). CVD can manifest as an acute or chronic condition and can affect any part of the central nervous system. Stroke is essentially a clinical term and is defined as an abrupt onset neurological deficit attributable to a focal vascular cause. Imaging studies and laboratory data are used to confirm the diagnosis and determine its etiology. Stroke is a heterogeneous entity and essentially is classified as ischemic and hemorrhagic. They will be the focus of this chapter.

Epidemiology

Stroke is the fifth leading cause of death and a major cause of adult disability in the USA [1]. A stroke occurs every 40 seconds nationwide, corresponding to nearly 800,000 cases annually. Of these, three quarters are first time strokes, and the remainder are recurrent events. There are 7.0 million estimated stroke survivors (prevalence of 2.5%) in the USA [2]. Despite data showing a decline in incident stroke, the number of strokes is projected to increase by 3.4 million by 2030 (20.5% increase in prevalence from 2012) due to advancing life span [3]. Every 4 min someone in the USA dies from a stroke. In 2017, stroke was responsible for about 150,000 deaths in the USA [1]. According to the World Health Organization (WHO) stroke represents the fourth leading cause of death in the low-income countries and the second cause worldwide [4]. The risk of having a stroke varies with race and ethnicity, but prevalence is higher in women than men across all races: white females 2.5% vs 2.4%, non-Hispanic black females 3.8% vs 3.1%, Hispanic females 2.2% vs 2.0%, and non-Hispanic Asian females 1.6% vs 1.1% [2]. In the USA, each year about 55,000 more females than males have a stroke [5]. Data from the Framingham Heart Study showed that women above age 55 had a significantly higher lifetime risk of stroke (17% vs 15%), primarily because women live longer [6].

Pathogenesis

The mechanism leading to impairment of blood flow in various areas of the brain is broadly classified into two types: ischemic and hemorrhagic. Stroke definition however does not distinguish between ischemic or hemorrhagic stroke or between subtypes of ischemic stroke.

Ischemic

Ischemic stroke is caused by a blood flow obstruction to the brain and accounts for 87% of all strokes [2]. Determining the cause of stroke as early as possible is essential, as it guides the decision for further management. TOAST stroke subtype classification (Trial of ORG 10172 in Acute Stroke Treatment) was introduced in 1993 primarily to allow investigators to report the effect of various treatments based on stroke etiological subgroups [7]. The original TOAST classification denotes five subtypes of ischemic stroke:

1. Large-artery atherosclerosis
2. Cardio-embolism
3. Small-vessel occlusion
4. Stroke of other determined etiology
5. Stroke of undetermined etiology

Hemorrhagic

Intracranial bleeding could be spontaneous or secondary to trauma (subdural hematoma, epidural hematoma); the latter group is not classified under stroke per se, although a stroke syndrome could occur from compression over the brain from outside or increased intracranial pressure (ICP). A hemorrhagic stroke occurs when a weakened blood vessel ruptures (e.g., aneurysm or AVM). The most common cause of spontaneous cerebral hemorrhage is uncontrolled hypertension.

There are two main subtypes of hemorrhagic stroke: intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). In ICH blood vessels rupture, and bleeding occurs within brain parenchyma, while in SAH blood vessels rupture,

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and bleeding occurs in the subarachnoid space. Neurological function is impaired by the mass effect exerted by hematoma on surrounding tissue, perihematomal edema and/or cerebral ischemia from associated vasospasm.

Risk Factors

Stroke risk factors have been reliably identified from prospective population-based studies such as the Framingham study. Risk factors are best thought of as modifiable and non-modifiable [8].

Non-modifiable include older age, sex, race/ethnicity, and genetic predisposition.

Modifiable stroke risks are multiple:

1. **Major** (most important and/or well described) hypertension, smoking, cholesterol, obesity, diabetes mellitus, metabolic syndrome, atrial fibrillation, structural cardiac abnormalities, atherosclerosis, prior stroke/transient ischemic attack (TIA), as well as smoking, sedentarism, alcohol, and socioeconomic class.
2. **Minor** (less described or less important): thrombophilia, oral contraceptive pills (OCP)/hormone replacement therapy (HRT), migraine, obstructive sleep apnea (OSA), homocysteine, diet, recreational drugs, infection, inflammation.

Prevention of Cerebrovascular Disease

Prevention of cerebrovascular disease includes primary and secondary prevention strategies.

Primary Prevention Strategies

Primary prevention includes measures to prevent or slow down development of cerebrovascular disease in those patients who did not suffer any stroke event.

Given the multitude of potential interventions, the long-term goal is to find a personalized approach to primary prevention. There is no ideal stroke risk assessment tool that would consider the effect of many potential contributory factors. However, the use of Framingham Stroke Profile and AHA/ASA CV Risk Calculator helps identify the individuals that may benefit from well-defined therapeutic interventions [9].

Below are evidence-based recommendations from American Heart Association/American Stroke Association Guidelines [9]. Only highest level of evidence is enumerated below:

1. Obtaining a detailed family history to identify the people who are at high risk of stroke.
2. Physical activity is recommended, being associated with a reduction in the risk of stroke. Adults should do at least 150 min/week (moderate intensity) or 75 min/week (vigorous intensity) aerobic physical activity.
3. Diet and nutrition are important lifestyle recommendations for stroke risk reduction. DASH-style diet (based on fruits, vegetables and low-fat dairy, low on saturated fat) is recommended to lower blood pressure. Reduced sodium intake and increased potassium intake (from fruits and vegetables contribution) lowers blood pressure and so the risk of stroke.
4. **Hypertension is the most important well-documented modifiable stroke risk factor.** Successful reduction in BP is more important than what specific agent is used to this goal. Patients should be screened annually for HTN and lifestyle modifications (as above).
5. Patients with prehypertension (SBP 120–139 mm Hg or DBP 80–89 mm Hg) should be discussed health-promoting lifestyle modifications. Patients with hypertension should be treated to target BP $<$140/90.
6. Self-measured BP monitoring is recommended to improve BP control.
7. Overweight (BMI 25–29 kg/ m2) and obese (BMI $>$ 30 kg/m2) individuals are recommended to lose weight in order to lower their BP as well as their risk of stroke.
8. Glycemic control in patients with diabetes is needed to reduce microvascular complications. In diabetic patients controlling BP to below 140/90 mm Hg and treatment with statin are recommended to reduce the risk of

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first stroke. It is unclear whether aspirin should be used in diabetic patients with low 10-year CVD risk for primary stroke prevention.

9. Smoking cessation by a combination of counseling and drug therapy (bupropion, nicotine replacement, or varenicline).
10. Smoking cessation in women suffering from migraine with aura should be strongly recommended. Alternatives to oral contraceptives (esp. those containing estrogens) might be considered in these women given their increased risk of stroke.
11. For patients with non-valvular AF with CHA2DS2-VASc score ≥ 2 and reasonably low risk of hemorrhagic complications, oral anticoagulants are recommended (warfarin INR 2–3, dabigatran, apixaban, rivaroxaban).
12. Closure of LAA can be considered in patients with high-risk AF who are not deemed suitable for long-term anticoagulation, if the risk of the procedure is acceptable.
13. Patients with asymptomatic carotid stenosis should be prescribed daily ASA, a statin, receive lifestyle counseling and be screened for other risk factors.
14. Referral of patients with atherosclerotic asymptomatic carotid artery disease above 50% for annual duplex ultrasonography monitoring and assessment of response to other treatment interventions is appropriate.
15. Screening low-risk population for asymptomatic carotid artery stenosis is not recommended.
16. For patients with valvular AF with CHA2DS2-VASc score ≥ 2 and reasonably low risk of hemorrhagic complications, long-term treatment with warfarin (goal INR 2–3) is recommended. Appropriate anticoagulation treatment in patients with valvular heart disease and no AF.
17. Appropriate referral for patients with sickle cell disease for prevention of stroke.
18. Counseling against unhealthy alcohol drinking.
19. Addressing illicit drug abuse.
20. Identifying patients with sleep apnea and referring for treatment.
21. Implementation of programs (e.g., in ED) to systematically identify and treat risk factors in all patients at risk for stroke is essential.

Secondary prevention includes measures in management of patients with cerebrovascular disease to prevent stroke recurrence and/or advancing vascular cognitive decline. The following sections of this chapter discuss this stage of prevention in more depth.

Ischemic Stroke and Transient Ischemic Attack (TIA)

Transient Ischemic Attacks

TIAs have been classically defined as stroke symptoms that resolve completely within 24 h. Most TIAs, however, last less than 1 h, and half of these are associated with acute infarction on brain MRI. With such advances in neuroimaging, a new TIA definition was proposed in 2002 to reflect tissue-based changes rather than duration of clinical symptoms. Currently, TIA is defined as a transient neurological dysfunction caused by focal ischemia of the brain, retina, or spinal cord, without MRI evidence of acute infarction, irrespective of the duration of symptoms [10, 11].

TIAs are heralds of ischemic stroke, as 10–15% are followed by a stroke within 90 days, and half of these happen in the first 48 h after TIA [12]. Urgent evaluation and treatment have been associated with up to 80% decrease in stroke risk after TIA [12]. Therefore, approach to the patients with TIA should include a thorough evaluation and identification of those patients with high risk of stroke after TIA [11, 12]. ABCD2 score is a well-validated tool to estimate risk of stroke after a suspected TIA considering age of 60 and above, presence of high blood pressure, clinical features of speech or motor impairment, duration of symptoms, and history of diabetes [13]. Because TIA patients experience only brief periods of painless neurological deficit, they may ignore their symptoms for days or weeks or may

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present to outpatient or urgent care setting instead of emergency centers, delaying their treatment. The pathophysiology of TIAs is identical to that of ischemic strokes (a serious transient blood clot), and recommended investigations are identical. Neuroimaging should be obtained within 24 h of onset of symptoms, preferably brain MRI. A noninvasive imaging of cerebral vessels should be done as part of a routine evaluation [11, 14]. There should be low threshold for hospital admission in patients with unreliable outpatient follow-ups for proper evaluation and monitoring [11, 14].

Ischemic Stroke

Most often the focal neurological symptoms suggesting a new stroke do persist, and when the brain MRI reveals underlying infarct, the patient is said to have suffered an ischemic stroke. Time to intervention from the onset of symptoms is very critical in the evolution and ultimately the outcome of ischemic stroke [15]. Over the last decade, several major changes in treatment have brought more hope to patients with acute ischemic stroke (AIS). However, the access to these therapies depends on patients arriving as early as possible to a specialized stroke care center. The American Heart Association (AHA)/American Stroke Association (ASA) has encouraged development and maintenance of public and medical education programs, as being essential to decrease the stroke onset to ED arrival times of the patients.

Prompt recognition of the signs and symptoms of stroke and increase use of EMS system (by calling 9–1-1 rapidly) leads to prompt evaluation of the stroke patients and increase in timely use of acute stroke interventions. Although progress has been made, still over a third of stroke patients fail to use Emergency Medical Services (EMS), leading to delay in acute stroke treatment [16].

The AHA/ASA's website is a great resource for both public and healthcare professionals for updated tools and information to increase stroke awareness [17]. In particular, the acronym **FAST** means to recognize *facial drooping*, *arm weakness*, and *speech impairment* as possible stroke symptoms, and if present then it is *time to call* for help by calling EMS [14, 17]. Other symptoms of concern may be summarized by the "five suddens"**:** sudden weakness and/or numbness of one part of the body, sudden confusion and trouble communicating, sudden imbalance, sudden severe headache, and sudden vision impairment [14, 17].

EMS will assess and transport the patient with positive stroke screen to the closest hospital that can administer iv thrombolysis and/or perform thrombectomy. These are "acute stroke ready," primary or comprehensive stroke hospitals, and their emergency departments function based on organized protocols aiming the most rapid evaluation of patients with suspected stroke. These stroke systems of care are continuously subjected to quality improvement processes to ensure evidence-based practices and improving patient care and outcomes [14]. Telemedicine solutions (Telestroke, Teleradiology) are increasingly used when on-site expertise is not available, and studies revealed that Telestroke use had no difference in mortality and functional outcome at 3 months, when compared to stroke centers [14].

Early Management of Patients with Acute Ischemic Stroke

Prehospital management of stroke patients focus on providing support to airway, breathing, and circulation as part of the adult cardiovascular life support (ACLS) program; oxygen supplementation, fluid administration in patients with hypotension, and hypoglycemia management if needed are being addressed [14]. In ED, obtaining a thorough past medical history, current medications and social history will assist the stroke team in differentiating a stroke from stroke mimics such as hypoglycemia, seizure disorder, migraine, delirium, psychosomatic disorder, alcohol and substance abuse, movement disorder, isolated cranial nerve palsy, and central nervous system neoplasm [14].

The neurological examination is focused on the National Institutes of Health Stroke Scale **(NIHSS),** a helpful tool used by healthcare

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professionals to assess patients with stroke symptoms rapidly, accurately, and reliably. Cardiovascular examination and looking for signs of coagulopathy are very pertinent in the acute assessment. On a side note, the blood pressure management principles differ between the types of stroke and are discussed in their respective sections later in the chapter.

NIHSS scale estimates patient's level of consciousness, orientation, attention, language, speech articulation, several cranial nerves function, motor function of each limb, ataxia, and sensory deficits and extinction. For details on the scale, please refer to the NIHSS website [18].

In principle the initial evaluation should be focused on determining whether the patient is eligible for acute reperfusion therapy. Time is brain in patients with AIS, meaning that early management is critical to optimize their outcome. Benefits of rtPA in AIS patients are time-dependent. AHA/ASA launched in 2010 Target: Stroke a national quality improvement initiative to reduce door-to- needle time to 60 min or less for eligible patients treated with iv rtPA. Since then the target has been moved to 45 min or less for rtPA start, and now goals extend to mechanical thrombectomy given its proven benefit in revascularization and patient outcomes [19].

Neuroimaging is fundamental to stroke management and helps determine if the stroke is ischemic or hemorrhagic. This is critical because the specific management of each type of stroke is different, and misdiagnosis can lead to severe consequences. The main modalities of neuroimaging are computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain. The choice of neuroimaging depends on availability and the condition of the patient. CT scan is equally effective to MRI in detecting acute intracranial hemorrhage, but it is often preferred as a more rapid test despite being associated with risk of radiation. However, diffusion-weighted MRI (DWI) is far superior to CT, having much higher sensitivity and specificity in detecting acute ischemia within minutes of the initial stroke symptoms [20]. MRI is also better in detecting subacute and chronic hemorrhages. Despite these advantages the higher cost of the investigation, unavailability of the machine at all centers, longer duration of procedure, claustrophobia, and various patient factors are limitations of MRI compared to CT scan [14]. Computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are providing essential information about intracranial and extracranial vasculature pathology, its potential role in stroke etiology and anatomical details important for possible endovascular intervention. CTA is a more rapid technique than MRA, but effects of radiation and contrast need to be considered.

Besides neuroimaging the stroke workup includes complete blood cell count, basic metabolic panel, blood glucose, blood alcohol level, urine drug screen, cardiac enzymes, coagulation tests, oxygen saturation, electrocardiogram, and cardiac monitoring [14]. However, the only required test result prior to initiating iv rtPA is blood glucose [14].

Blood Pressure Management

Hypotension and hypovolemia should be corrected promptly to maintain adequate cerebral and organ perfusion pressure. In patients who are candidates for iv thrombolytic therapy and/or mechanical thrombectomy – elevated BP needs to be carefully lowered and maintained to SBP $\leq$ 185 and DBP $\leq$110 before the procedure is initiated. Thrombolytics are contraindicated if BP cannot be maintained below 185/110 [14]. During the intervention and for 24 h after, BP should be maintained below 180/105. Intravenous agents such as labetalol, nicardipine, clevidipine, and, if BP is refractory, sodium nitroprusside, are being used to lower BP to target [14]. In patients who are not candidates for acute reperfusion therapy, lowering SBP $\leq$ 220 and DBP $\leq$ 120 is reasonable, aiming to lower BP approximately 15% of baseline BP during first 24 h after onset of stroke. Occasional patients may require more aggressive lowering of BP (e.g., acute MI, acute heart failure, aortic dissection, post -thrombolytic sICH, preeclampsia/eclampsia) [14].

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Intravenous Thrombolysis

Alteplase (tPA, rtPA) is the only FDA-approved fibrinolytic agent used for the treatment of AIS. The National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study showed intravenous rtPA as clearly beneficial in improving clinical outcome when used within 3 h of onset in selected patients with AIS [21]. Alteplase is a serine protease that binds to fibrin inside a blood clot and initiates conversion of plasminogen to plasmin, increasing the chance of cerebral revascularization. The treating dose is 0.9 mg/kg (total dose not exceeding 90 mg) over 60 min [21]. The bolus dose is administered as 10% of the total dose over 1 min. To date FDA has only approved rtPA for use within 3 h of stroke onset. However, randomized controlled trials showed benefit of thrombolysis with rtPA in AIS patients up to 4.5 h and AHA/ASA guidelines currently recommend a 4.5 h window for rtPA administration [14, 22]. More recently, **tenecteplase** has shown promising results and may become a preferred alternative to rtPA. A single bolus of 0.4 mg/kg (maximum 25 mg) might be considered in AIS patients with minor neurological impairment and no evidence of large vessel occlusion. Per AHA/ASA guidelines, a dose of 0.25 mg/kg tenecteplase may be chosen over rtPA to be administered in patients eligible for mechanical thrombectomy, given higher rate of revascularization achieved [23]. Tenecteplase is a bioengineered variant of rtPA with greater fibrin specificity, longer half-life and increased resistance to tissue plasminogen inhibitor-1 than rtPA. The greatest benefit from iv thrombolysis is derived when administered in the first 90 min from symptom onset, so it is critical not to delay initiation of rtPA. Eligibility criteria have evolved, and contraindications for iv rtPA have been recently revisited in the most recent AHA/ASA guidelines [14]. Subsequently, more patients can be considered for thrombolysis after careful individualized clinical judgment.

Individuals over 18 years of age diagnosed with ischemic stroke with disabling neurological deficit, with symptoms onset within 4.5 h or wake-up stroke and DWI-FLAIR imaging mismatch on MRI, are considered for acute thrombolytic therapy.

Absolute contraindications (because of no benefit or potential harm) include [14]:

1. Presence of acute intracranial hemorrhage on the initial head CT
2. History of intracranial hemorrhage
3. Symptoms and signs suggesting subarachnoid hemorrhage
4. Mild non-disabling stroke (NIHSS score 0–5)
5. Prior ischemic stroke or severe head trauma within 3 months
6. Acute in-hospital phase of head trauma
7. Intracranial/intraspinal surgery within 3 months
8. Extensive regions of clear hypoattenuation on initial head CT
9. SBP $\geq$ 185 or DBP $\geq$110 than cannot be lowered and maintained
10. Coagulopathy including platelet count $<100{,}000/mm^3$, elevated aPTT >40 s, INR >1.7, PT >15 s
11. Full treatment dose of LMWH within previous 24 h
12. Current use (last 48 h) of direct thrombin inhibitors or direct factor Xa inhibitors
13. Symptoms consistent with infective endocarditis
14. Suspected aortic arch dissection
15. Intra-axial neoplasm, AVM, or giant aneurysm
16. GI malignancy or GI bleeding within 21 days
17. Active internal bleeding

Relative contraindications now include [14]:

a. Pregnancy.
b. Seizure at onset of symptoms.
c. Blood glucose levels <50 or > 400 that can be corrected, and patient maintains eligibility.
d. Major surgery or serious trauma (not involving the head) within 2 weeks.
e. Presence of cerebral microbleeds (CMBs) on prior brain MRI.
f. Small or moderate unruptured and unsecured intracranial aneurysm.
g. Acute or recent MI within 3 months.
h. Rapidly improving stroke symptoms.

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After iv rtPA administration patient should be admitted to ICU or stroke unit for monitoring.

Neurological assessments and BP measurement are performed every 15 min for first 2 h, every 30 min for the next 6 h, and then hourly to 24 h. Should patient develop severe headache, acute hypertension, nausea or vomiting, or worsening neurological deficit, the infusion needs to be stopped (if still being infused) and emergent head CT obtained. Otherwise a head CT or MRI scan must be obtained at 24 h, before starting antiplatelets or anticoagulation.

Endovascular Treatment

Recent studies have conclusively demonstrated the benefit of mechanical thrombectomy performed in selected patients with AIS up to 24 h from onset of symptoms. The strongest level of evidence we have is for causative ICA or MCA M1 segment occlusion in patients who also meet the following criteria: age $\geq$ 18, mRS 0 or 1, NIHSS $\geq$6, ASPECTS $\geq$6, and treatment initiated within 6 h from stroke onset [24]. For selected patients with AIS within 6 to 16 h of last known normal and causative large vessel occlusion (LVO) in the anterior circulation and who also meet other DAWN and DEFUSE3 trials eligibility criteria, mechanical thrombectomy is recommended [25, 26]. Based on DAWN trial eligibility criteria and results, patients with AIS within 16–24 h of last seen normal and LVO in the anterior circulation are also considered for mechanical thrombectomy [26]. During and following mechanical thrombectomy, a reasonable BP to maintain is below 180/105.

Although other modalities could be considered to achieve the best reperfusion results, (e.g., intra-arterial thrombolysis, MERCI device, balloon guide catheter), stent retriever is the preferred device and is indicated as first-line therapy.

Antiplatelet Therapy

Aspirin 75–325 mg is recommended for patients to take orally within 24 to 48 h of stroke onset [14].

However, following iv rtPA administration, antiplatelet therapy is generally delayed for 24 h, unless patients have another indication for it, and the risk of not taking it is higher than the risk of bleeding.

In patients who did not receive iv rtPA and have a minor stroke (NIHSS$\leq$3) of undetermined etiology or high-risk TIA, dual antiplatelet therapy (ASA and clopidogrel) is recommended for 21 days to reduce the risk of recurrent ischemic events and mainly ischemic stroke [27, 28]. Per SAMMPRIS trial results, patients with AIS secondary to severe intracranial stenosis benefit from 3 months of dual antiplatelet therapy, followed by monotherapy [29]. Ticagrelor is not recommended over aspirin for treatment of minor ischemic stroke patients [14].

Role of Other Therapies in Acute Setting

Urgent anticoagulation treatment is not recommended for patients of acute ischemic stroke, and their usefulness in patients with internal carotid artery stenosis is not established [14]. The usefulness of emergent or urgent CEA/carotid angioplasty and stenting in patients with critical carotid stenosis or occlusion and unstable neurological status is not well established. To date, no pharmacological or non-pharmacological agents have shown benefit as neuroprotectors. The benefit of induced hypothermia in AIS is uncertain and should only be considered as part of clinical trials.

Other Considerations

Early during hospitalization patients are screened for dysphagia before they start eating, drinking, or receiving oral medications. Dysphagia is common poststroke and risk factor for aspiration pneumonia. In patients who are unable to swallow safely, enteral diet should be started within 7 days of AIS [14].

Persistent hyperglycemia in the first 24 h after AIS is associated with worse outcomes, and the

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recommended blood glucose is 140–180 mg/dl range with close monitor to avoid hypoglycemia [14].

If patients are febrile above 38C, they should receive antipyretics and the source of hyperthermia identified and treated, given increased risk of in hospital death outside normothermia.

Patients with stroke are best cared for in specialized stroke units that were shown to reduce their morbidity and mortality. Stroke units use standardized order sets that implement the best practices and employ rehabilitation services early during hospitalization.

In the stroke unit, patients undergo cardiac monitoring to screen for atrial fibrillation. Also, they are subjected to protocolized neurological exams and receive rehabilitation (physical, occupational, speech/language therapies) based on tolerance and anticipated benefit.

Continuation of statin therapy during hospitalization of patients with AIS is recommended.

In case of symptomatic severe carotid stenosis, patients should be evaluated for urgent CEA/angioplasty and stenting within 2 weeks of stroke ideally [30]. CTA or MRA should be obtained within 24 h in patients with AIS in the anterior circulation territories who are candidates for CEA or stenting.

Complications

Orolingual angioedema is a rare but potentially life-threatening complication of rtPA. The risk is higher in patients taking ACE inhibitors. Treatment consists of diphenhydramine (50 mg iv), ranitidine (50 mg iv), and dexamethasone (10 mg iv).

Approximately, one fourth of the patients with ischemic stroke will develop complications. The most common complications following AIS are (with incidence in parenthesis): brain edema (33%), intracranial hemorrhage (10%), recurrent ischemia (11%), and seizures (<10%). Brain swelling leads to increased intracranial pressure and further neurological deterioration and is associated with high risk of mortality. Most patients develop brain swelling in the first 48 h, but close monitoring of patients for 5 days post MCA infarctions is warranted [31]. Moderate hyperventilation and osmotic therapy can be used initially, but decline in level of consciousness indicates need for neurosurgical intervention with decompressive craniectomy.

Secondary Prevention of Stroke

The purpose of various investigations in the acute hospital setting of patients with AIS is to establish the most likely cause of the stroke and implement promptly secondary prevention measures including the most appropriate antithrombotic therapy and/or surgical interventions, if needed. Modifiable risk factors discussed previously in this chapter need to be addressed for secondary stroke prevention as well.

Antiplatelets are the mainstay of stroke prevention in non-cardioembolic stroke, and their choice in the acute setting should be individualized. Aspirin (50–325 mg daily orally), clopidogrel (75 mg by daily orally), and ASA (25 mg)/extended-release dipyridamole (200 mg) are reasonable choices for secondary stroke prevention [32]. Triple antiplatelet therapy was shown to be harmful and should not be administered. CTA or MRA will help select the patients with carotid artery disease for potential CEA/stenting and detect patients with severe intracranial stenosis that would benefit from dual antiplatelet therapy (DAPT). If revascularization is indicated, it is preferable that the procedure be performed within 2–7 days from the index event rather than more delayed intervention [30]. When the stroke is due to atrial fibrillation, anticoagulation can be initiated 4–14 days after AIS.

All patients are screened for DM using HgA1c and have their lipid profile checked to determine baseline LDL-C and assess the ASCVD risk. Adherence to lifestyle changes and effects of lipid lowering medications should be assessed at 4–12 weeks and then every 3–12 months. However, routine testing for thrombophilia, hyperhomocysteinemia and OSA is not recommended in patients with AIS. Smoking cessation must be reinforced as well as other behavioral modifications as discussed. With regard to hyperlipidemia, any adult over age 20 should have lipids checked

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to assess their atherosclerotic cardiovascular disease (ASCVD) risk. AIS survivors should watch diet, exercise, and take appropriate medicines to address hyperlipidemia and follow up regularly with their primary care provider to assess the results of these efforts. A follow-up fasting lipid profile test in 4–12 weeks after initiation of statin or its dose adjustment is recommended; this should be followed by periodic lipid testing at least annually to monitor adherence and safety. Patients age 75 years or younger, with clinical ASCVD (that includes AIS), should have hyperlipidemia managed with high-intensity statin with goal of reduction of LDL cholesterol by at least 50%. If there are any concerns on high-intensity statin use due to side effects or contraindications, moderate-intensity statin can be considered with goal of 30–49% reduction of LDC cholesterol [14]. Stroke education is very important and recommended. Patients should receive information, advice, and provided opportunity to talk about the impact of the illness on their lives [14].

Intracerebral Hemorrhage (ICH)

One in every ten strokes is caused by intracerebral hemorrhage (ICH) [2]. Up to 50% of all patients with ICH die within a month, and most deaths occur during the initial hospitalization [33, 34]. Prompt and excellent medical care is associated with improved morbidity and mortality. The symptoms and signs of ICH are strongly influenced by the location, size, and pattern of extension of bleeding. Severe sudden onset headache, coma, vomiting, seizures, and neck stiffness are manifestations of the largest hemorrhages. Patients with deep, small hematomas may never develop headache as part of their illness, and their focal neurological signs may be indistinguishable from those of ischemic strokes [35].

Head CT is the gold standard for distinguishing ischemic stroke from ICH, and MRI of the brain helps to determine the age of the hematoma. CT angiography (CTA) and contrast-enhanced CT are excellent tools to identify early the patients at risk for hematoma expansion, while serial head CT scans are more practical to monitor expansion of ICH during hospitalization. MRI with gadolinium, MR angiography (MRA), and MR venography (MRV) are useful tests to evaluate for underlying structural pathologies such as arteriovenous malformations (AVM) and brain tumors if there is clinical or radiological suspicion [37]. The decision to obtain a conventional cerebral angiography (DSA) early during ICH management is made on a case by case basis.

The most common cause of ICH is hypertension, but even in the absence of such history, many patients present with elevated BP on admission, and it is difficult to determine if their BP reflects elevated intracranial pressures (ICP) or chronic uncontrolled hypertension. Eliciting promptly a history of antithrombotic medications (antiplatelets, anticoagulants) and/or medical conditions associated with coagulopathies (liver disease, cancer, hematologic disorders) is critical given the high morbidity and mortality associated with abnormal hemostasis. Additional history about seizures; baseline cognitive and neurological status; vascular risks such as HTN, DM, and smoking; prior strokes; illicit drugs as well as stimulants (including diet pills); and sympathomimetics is very important as well.

A history of dementia can raise suspicion for amyloid angiopathy that is another major cause of ICH.

Presence of ICH in a female patient younger than 65 with no history of HTN, smoking, or coagulopathy and evidence of lobar hematoma and/or intraventricular extension raises probability of underlying vascular malformation.

Initial blood and urine tests should include PT/INR and aPTT, CBC, electrolytes, glucose, BUN, creatinine, troponin, and urine toxicology as well urinalysis/urine culture.

Just like in the case of ischemic stroke, the patient's airway patency and cardiovascular support are primary objectives, before specific management is initiated. Every ED should be prepared to manage patients with ICH or have a plan for rapid transfer to a stroke center with neurology, neurosurgery, and neuroradiology expertise, as well as critical care unit nursing staff capable to care for these patients. Consults via Telemedicine in ED can be a valuable

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alternative for the hospitals with no on-site consultants [37].

The key treatment goals in patients with ICH are halting expansion of hemorrhage by controlling BP and correcting any coagulopathy, as well as assessing necessity for surgical intervention [37].

A baseline standardized severity score such as ICH score, Glasgow Coma Score, and NIHSS should be obtained to streamline communication between providers. However, they are not meant to provide prognostic information and should not be used as a primary method to predict outcomes in patients with ICH. They should not direct treatment modalities either. These prediction models based on patient's age, GCS, hematoma volume, and location did not consider the impact of limitation of care early during ICH evolution [37]. Thus, caution is urged when providing prognostic information early in the course of ICH, particularly if this prognostication is used to guide limitation of care. The newest guidelines stress the importance of aggressive medical and surgical care early after ICH onset and deferring prognostication until at least second full day of hospitalization [37].

Up to 20% of ICH occur in patients on anticoagulation and are associated with higher mortality [38]. Patients with known coagulation factor deficiency or severe thrombocytopenia should receive appropriate replacement therapy [37]. At this point it is unclear whether patients on antiplatelet therapy should receive platelet replacement, but it was shown that these patients are at risk for early mortality as well [38]. Protamine sulfate has been used to reverse coagulopathy in patients on iv heparin at the time of ICH and may be considered [37].

Vitamin K antagonist-associated (VKA) ICH with elevated INR requires rapid administration of intravenous vitamin K, but that does not reverse the coagulopathy fast enough. Thus, use of other treatment strategies is necessary, and prothrombin complex concentrates (PCC), activated PCC factor VIII inhibitor bypassing activity (aPCC FEIBA), and fresh frozen plasma (FFP) are considered to replace vitamin K-dependent factors. Studies showed that PCCs achieve a more rapid INR reversal than FFP and may be preferred. rFVIIa is not currently recommended for warfarin reversal, and studies showed no clinical benefit in ICH not associated with oral anticoagulants (OAC) either (due to increased risk of thromboembolism). Data on reversal of NOAC is limited. PCC may be useful for rivaroxaban and apixaban, while rFVIIa or FEIBA may be helpful for dabigatran [37]. Hemodialysis is an option for dabigatran as well.

Patients with ICH and impaired mobility are at high risk for developing DVT and PE. Thus, pneumatic compression of legs should be initiated on the first day of hospitalization for prevention of DVT. Only after cessation of intracranial bleeding cautious use of anticoagulants as prophylaxis for thromboembolism can be considered, usually 2–4 days after onset. In cases with high bleeding risk, inferior vena cava (IVC) filter placement is widely used to prevent progression of DVT to PE [37].

High systolic BP is associated with greater hematoma expansion, neurological deterioration, and death and dependency [37]. However, blood pressure management in acute ICH has been the subject of controversy for decades, particularly related to concern of possible hypoperfusion in the region of edema surrounding the hematoma.

Recent smaller trials showed that acute aggressive reduction in BP within 3–6 h of ICH onset was safe, appeared to reduce the hematoma growth, and was not associated with adverse events [37]. The results of INTERACT2 a large randomized trial that enrolled patients with mild-moderate ICH and SBP 150–220 revealed that intensive BP lowering (SBP < 140) lead to no significant decrease in death or serious adverse events (SAE) and no significant reduction in hematoma growth but demonstrated improved functional outcome and better quality of life at 3 month [39].

There is less data for patients with SBP above 220, but the guidelines at this point suggest aggressively lowering BP with continuous iv infusion and frequent BP monitoring [37].

Patients with ICH require admission to an intensive care unit (ICU) and close monitoring of their hemodynamic status, intracranial pressure

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(ICP), cerebral perfusion pressure (CPP), neurological status, and possible seizures [37]. Care in an ICU by physicians and nursing with neuroscience expertise was associated with lower mortality.

About half of deaths after stroke are attributed to medical complications such as pneumonia, respiratory failure, pulmonary embolism, and sepsis. Protocolized screening for dysphagia has been shown to decrease the risk of pneumonia and should be performed in all patients prior to any oral intake.

Elevated blood glucose on admission predicted poor outcome and increased mortality, independent of diabetes. It is recommended that both hyperglycemia and hypoglycemia be avoided [37].

Fever is a common encounter after ICH, especially with intraventricular hemorrhage. In the absence of strong supportive data, it may be reasonable to treat fever after ICH.

Less than 10% of patients develop seizures in the first 24 h post-ICH and studies of continuous EEG monitoring reported up to 30% risk of electrographic seizures even in patients on prophylactic anticonvulsants [37]. The most important predictors of seizures are young age and lobar location of hematoma [40]. It was shown that prophylactic anticonvulsants could be associated with increased mortality (e.g., phenytoin), but clinical seizures should be treated [41]. Overall prophylactic use of antiseizure medications has not been shown to be beneficial, and they are not recommended [37].

Patients admitted for ICH need to be screened for myocardial ischemia/infarct with EKG and cardiac enzyme testing. Other complications include hyponatremia, impaired nutritional status, acute renal injury, gastrointestinal bleeding, and poststroke depression, and these should be screened and managed as needed.

Data regarding frequency of elevated ICP in patients with ICH is scarce, but it seems to be more common in young patients and those with supratentorial hematomas. Elevated ICP is caused essentially by the mass effect from hematoma and surrounding edema and/or hydrocephalus from IVH. ICP can be measured by a ventricular catheter (that allows CSF drainage and reducing ICP) or parenchymal ICP devices. Thus far, however, there is no clear evidence that management of elevated ICP improves outcome after ICH.

Most of the indications for management and treatment have been extrapolated from TBI literature and include GCS $\leq$8, clinical evidence of transtentorial herniation and significant IVH or hydrocephalus. Ventricular drainage is considered particularly in those with decreased level of consciousness. The goal is maintaining ICP $<$ 20 mm Hg and CPP of 50–70 mm Hg. Several strategies are used in ICU for ICP lowering including elevation of head of bed to 30°, mild sedation, osmotic therapy (mannitol, hypertonic saline), CSF drainage, and hematoma evacuation/decompressive craniectomy [37]. Corticosteroids should not be used as treatment for elevated ICP in ICH.

A special category is represented by patients with cerebellar hemorrhage who may be deteriorating neurologically, have brainstem compression and/or hydrocephalus from ventricular obstruction, and require prompt neurosurgical intervention to remove hematoma.

At this point the benefit of minimally invasive (stereotactic or endoscopic) surgical evacuation of IVH in terms of long-term morbidity and mortality benefits is uncertain.

Rehabilitation is started as soon as the patient is stable for mobilization and is continued in rehabilitation facilities or outpatient setting. Home-based rehabilitation programs were shown to be cost-effective and produce results comparable to conventional outpatient rehabilitation [37].

Patients with ICH are at high risk for recurrent major vascular events, and this risk is highest in the first year (cumulative risk is 1–5% per year). Risk factors for recurrence include lobar hemorrhage, older age, ongoing anticoagulation, presence of microbleeds on GRE MRI, and presence of APO e2 or e4 alleles.

Relationship between hypertension, smoking, heavy alcohol use, cocaine use, and ICH are well established, and these risk factors need to be addressed. BP optimization efforts should begin immediately after ICH, and recommended long-term goal for BP control is below 140/90.

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Treatment of OSA is likely to be beneficial as well.

In terms of resuming antithrombotic therapy after ICH, antiplatelet agents appear to be generally safe. Anticoagulation should be avoided though after lobar hemorrhage, but it can be considered in patients after deep ICH if the risk of thromboembolism is particularly high and BP is adequately controlled.

At this point there is insufficient data to strongly recommend restricting use of statin in ICH patients.

Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhages represent 3% of all strokes, and most of them are due to the rupture of a cerebral aneurysm (85%) [2]. Aneurysmal SAH (aSAH) is a devastating type of stroke with mortality up to 45% and significant morbidity among the survivors [42]. Fifteen percent are non-aneurysmal SAH; their cause is often not identified even after extensive investigation [43]. Some may be due to a vascular malformation, and others, called perimesencephalic SAH, have a specific distribution and excellent prognosis compared to aneurysmal bleeds [43]. Incidence of aSAH increases with age (most common at age 40–60), and it is 1.2 times more common in women than men. Non-modifiable risk factors are female gender, history of prior aSAH, and family history of intracranial aneurysm (IA) or aneurysmal bleed [42]. Modifiable risk factors for aSAH include hypertension, smoking, alcohol abuse and cocaine use. Smoking cessation, cutting down alcohol, treatment of hypertension, and diet rich in vegetables may help prevent aSAH [42].

Sometimes intracranial aneurysms (IA) are found incidentally on cerebrovascular imaging studies. Unruptured intracranial aneurysms (UIA) are common (estimated 3.2% in the general population), but the overall risk of rupture is relatively low (approx. 0.25%). The larger aneurysms and those located in the posterior circulation (vertebrobasilar arteries), including posterior communicating artery, were shown to be at higher risk of rupture [42]. Although aneurysmal size of more than 7 mm is more prone to develop SAH, risk factors like smoking, alcohol, and psychosocial stress can increase the risk of rupture regardless of size [44–46]. UIA will need periodic monitoring, and the management decisions are usually made by a team including a vascular neurologist, vascular neurosurgeon, and interventional neuroradiologist. Routine screening for UIA in the general population is not recommended. However, CTA or MRA screening with adequate prior counseling of the patient may be considered in first-degree relatives of those with sporadic SAH and is appropriate in families with more than one member affected with IA and in those with family history of IA and evidence of autosomal dominant polycystic kidney disease, Ehlers-Danlos type IV or other predisposing conditions.

SAH should be the primary diagnosis of any patient presenting with acute onset severe headache until proven otherwise. 80% of patients present with "the worst headache of life," but many are often misdiagnosed, especially those presenting with "sentinel bleed" [42]. Other symptoms include nausea/vomiting, stiff neck, loss of consciousness, and focal neurological deficits.

Most SAH will be diagnosed with a non-contrast head CT (NHCT). The sensitivity is not 100% though, and if the initial CT scan is inconclusive, an evaluation of cerebrospinal fluid after lumbar puncture will help with the diagnosis. Other imaging modalities include CT angiography, digital subtraction angiography (DSA), and brain MRI which will assist in further management.

Treatment involves neurosurgical clipping or endovascular coiling of the ruptured aneurysm. These treatment techniques were compared in the International Subarachnoid Aneurysm Trial (ISAT), and combined 1-year mortality and morbidity were significantly greater in the surgically treated patients compared to endovascular technique (30.9% vs 23.5%; ARR 7.4%, $P = 0.00001$), mainly on the account of disability rates [47].

Given the high risk of early preoperative rebleeding, treatment should be performed as early as possible to reduce this risk. Most of the

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rebleeding occurs within 12 h of first bleed and is associated with high mortality. Although there is no established cutoff blood pressure as a treatment goal, AHA/ASA guidelines recommend maintaining SBP under 160 mmHg to reduce the risk of rebleeding, based on expert consensus [42]. Limited studies have shown benefit of short-term treatment with antifibrinolytic therapy (tranexamic acid or aminocaproic acid) to reduce rebleeding when there is a delay in aneurysm obliteration, but these agents are not FDA-approved for such indication [42, 48].

Cerebral arterial vasospasm leading to delayed cerebral ischemia (DCI) is a major cause of disability and death after aSAH. Vasospasm occurs usually 4–10 days after aneurysm rupture and resolves spontaneously after 21 days. Controlled studies on SAH management demonstrated no benefit on outcome from traditional hemodynamic augmentation of triple-H therapy (hemodilution, hypervolemia, and hypertensive therapy) [42]. Nimodipine, a calcium channel blocker, has been found to improve outcome in patients with aneurysmal bleed and is therefore recommended in all patients with aneurysmal SAH, unless contraindications are present [49].The mechanism of action by which the drug prevents DCI is unclear, but it has not been shown to reduce cerebral vasospasm as initially predicted. Hemodynamic stability by maintaining normal volume status of the body and induction of hypertension (if needed) are also recommended to prevent DCI [50]. A recent meta-analysis showed a significant benefit of cilostazol in reducing risk of symptomatic vasospasm, cerebral infarcts, and poor outcome suggesting clinical usefulness in preventing DCI [51]. Acute hydrocephalus in aSAH is usually managed by external ventricular drainage and less often by lumbar drainage [42].

Early seizures occur in 6–18% of patients and nonconvulsive seizures are not uncommon in the comatose patients. Short-term prophylactic antiepileptic medications are commonly used despite no high-quality evidence for benefit, and we need to be mindful to potential risks associated with these medications [52]. However, routine long-term continuation of anticonvulsants is not recommended.

Following discharge, these patients should be followed up closely to minimize their risk factors, and it is reasonable to refer them for a comprehensive cognitive, behavioral, and psychosocial evaluation [42].

Rehabilitation of Patients with Stroke

Restorative therapies play an important role to improve quality of life and functional outcome of stroke survivors. Measures of rehabilitation include prevention of complications, and it starts during the acute hospitalization. An initial evaluation by multiple disciplines: physical therapy, speech and language therapy, occupational therapy, physical and rehabilitation medicine, dietician, behavioral health, etc., is recommended to start during the initial hospitalization itself [53]. Before the patient is discharged following an acute stroke, a formal assessment of the following is important: activities of daily living (ADL), instrumental activities of daily living (IADL), communication abilities, functional mobility, as well as screening of cognitive deficits, and dysphagia screening need to be obtained to adequately plan rehabilitation interventions [53, 54].

Post-acute rehabilitation care of patients can take place in different settings as guided by the stroke survivor's recovery needs, potentials, and goals. The patients who continue to need hospital-level care can participate in intense therapy for at least 3 h a day for 5 days a week; an appropriate disposition after discharge will be "inpatient rehabilitation facility" (IRF). For other patients who have complex acute and chronic medical needs to address, a suitable disposition can be "long-term care hospital" (LTCH) or "long-term acute care" (LTAC) facility. Subacute rehabilitation in "skilled nursing facility" (SNF) would be indicated for patients who do not have potential to perform intense therapy but have skilled nursing needs (e.g., skin breakdown, bowel/bladder impairment), close monitoring requirements for health conditions, impaired ADL and IADL, nutritional deficits, and complex rehabilitation needs due to spasticity or pain management. If these medical and neurological disabilities interfere

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significantly with performance of ADL and IADL, the patient may need to be transitioned to a "long-term care" (LTC) facility. Some stroke survivors can eventually be transitioned to home but may require skilled healthcare oversight and intervention at home by "home healthcare" (HHC) team. Most patients discharged to home can continue their therapy needs by following up with outpatient rehabilitation services. Rehabilitation strategy should also include interventions to prevent skin breakdown and contractures; prevention of deep venous thrombosis; treatment of bowel and bladder incontinence; assessment, prevention and treatment of pain after stroke; fall prevention; assessment, evaluation, and treatment of poststroke mood disorder; and secondary stroke prevention [53].

Various disciplines play important roles in the rehabilitation of patients with stroke. These include nursing, physical therapy, occupational therapy, speech and language therapy, physician medicine and rehabilitation, neurology, primary care, social work, psychology, psychiatry, and counseling. Stroke survivors, who are suitable candidates for post-acute care, should receive an organized, coordinated, interprofessional approach for rehabilitation [53]. Coordination and communication among various disciplines is key, and primary care is positioned to facilitate this, while focusing on management of chronic illnesses and prevention of complications.

Key Considerations [53, 55]

- Stroke is a chronic disease with impact long beyond the acute phase of the illness.
- Rehabilitation of stroke patients should be addressed by a multidisciplinary team that follows seamless communication and coordination.
- Following up on any swallowing difficulties and addressing nutritional needs are important for poststroke patients.
- One third of the stroke survivors have cognitive impairment at 3 months and 12 months after stroke. Hence screening and monitoring of cognition are important.
- Proper positioning, therapy, and management of weak extremity and joint to prevent contractures and spasticity. Spasticity, imbalance, and ataxia are some examples of the complex sequelae of stroke that needs evaluation and management. Proactive fall precautions are recommended.
- Proactive care to prevent and treat skin ulcers.
- For prevention of deep venous thrombosis and pulmonary embolism, continuous anticoagulation therapy for the duration of acute hospital stay and throughout the rehabilitation or until mobility is regained. For those where anticoagulation therapy is contraindicated, mechanical methods are recommended.
- Assessing and addressing issues of bowel and bladder incontinence following stroke throughout rehabilitation process is an important method to prevent complications and improve quality of life.
- Assessment and management of poststroke pain complications should be addressed with pharmacological and non-pharmacological approach. Shoulder pain and central poststroke pain syndrome can be a serious barrier for rehabilitation efforts.
- Seizure prophylaxis is not recommended for stroke patients, and any new seizure should be investigated and managed per standard recommendations.
- Screening for depression should be routinely done. Behavioral approaches and pharmacological therapy can be utilized for addressing poststroke depression and emotional distress.
- Other considerations in rehabilitation include addressing sensory impairments such as touch, hearing, and vision, osteoporosis screening and prevention measures for appropriate poststroke patients, disability assessment, and evaluation for appropriate durable medical equipment.

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Movement Disorders

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Douglas J. Inciarte and Diego R. Torres-Russotto

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Introduction

Movement disorders (MDS) are neurological diseases caused by dysfunction of the motor control systems. They are extremely common, with an overall prevalence in the general population of more than 20%. However, these disorders are vastly underdiagnosed and therefore undertreated. Movement disorders are classified as hypokinetic (those associated with paucity of movement like the bradykinesia in parkinsonism) and hyperkinetic (those with excessive movement, like in tremors, dystonia, and tics). There are about 30 different types of movement disorder phenomenologies (Table 1). Each of these phenomenologies or clinical phenomena are the external expression a number of different diseases. For example, bradykinesia is a hypokinetic phenomenology, and it is the hallmark of different parkinsonian disorders like Parkinson disease (PD), progressive supranuclear palsy (PSP and Multiple Systems Atrophy (MSA).

Initial Diagnostic Considerations

The first step in the evaluation of any movement disorder is to recognize the movement phenomenology, so to be able to generate a list of the different etiologies that share it – the differential diagnosis [1]. Jumping straight to the differential leads to misdiagnoses. This might be why 30–50% of cases with action tremors are misdiagnosed [2]. For example, a patient presenting with a head shaking could be hastily thought as to having essential tremor (ET). But if the physician determines first the phenomenology, could find that it is a dystonic tremor, leading to a completely different set of possible etiologies (spasmodic torticollis, tardive dystonia, etc. Table 1).

Table 1 Common movement disorders phenomenologies and some of their usual diseases

Phenomenologies	Associated diseases
Bradykinesia	Parkinson disease, progressive supranuclear palsy, multiple systems atrophy, dementia of Lewy bodies
Muscle stiffness	Stiff person syndrome
Akathetic movements	Medication-induced acute akathisia, tardive akathisia
Ataxia	Friedrich's ataxia, spino-cerebellar ataxias, multiple systems atrophy
Chorea	Huntington's disease, dopaminergic drug-induced dyskinesias in PD
Dystonia	Primary or secondary cervical dystonia, Blepharospasm, writer's cramp
Tics	Tourette syndrome
Tremor	Essential tremor (ET), ET-Plus, medication-induced tremor

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Importance of Movement Disorders

- Some are curable, but all are treatable.
- There are many good treatment options: oral medications, botulinum toxin injections, intrathecal baclofen pump, deep brain stimulation, etc.
- Prompt diagnosis and proper treatment DOES improve quality of life.
- Frequently misdiagnosed or undiagnosed and therefore untreated.
- Some patients suffer for many years before they are given a diagnosis.

Initial Work-up

There are a number of treatable and curable conditions that present as movement disorders. Therefore, once the physician has identified a movement phenomenology, the next step is to rule out curable conditions that could cause them. In movement specialty centers, most patients undergo the battery of tests listed on Table 2. Wilson's disease is associated with copper deposition in the liver and basal ganglia. If a patient presents with any movement disorder under the age of 50, Kayser-Fleischer rings on ocular examination, or abnormal liver function studies, they should undergo further testing for Wilson's disease as this could be effectively treated with chelation [16].

Some of these treatable conditions could both cause the MDS and could make a baseline MDS worse. A good example of this dual effect is tremor and hyperthyroidism. Although not a disease, pregnancy is an important condition to keep in mind, as it can cause tremors, chorea gravidarum and exacerbate other MDS. Importantly, every patient presenting with dystonia or parkinsonism deserves a trial of carbidopa/levodopa as this could be the practical cure for a group of rare genetic conditions called dopamine-responsive dystonias.

Also, consideration of medication-induced MDS is important, as these are common and frequently under-diagnosed. Typical drugs associated with MDS include lithium, antidepressants, gabapentin and other antiepileptics (myoclonus, tremor, ataxia), dopamine blockers like metoclopramide and antipsychotics (dystonia, tremor, parkinsonism, ataxia), and many others.

Parkinson Disease

Parkinsonism is a syndrome characterized by the presence of bradykinesia associated with resting tremor, rigidity, or postural instability.

Table 2 Initial work-up in movement disorders and their associated condition

Diseases to rule-out in MDS patients	Initial work-up	Typical movement disorders
Wilson's disease	Ceruloplasmin, 24 hrs urine copper level	Need to consider it in any movement phenomenology
Hyper- and hypothyroidism	TSH, T4	Tremor, chorea, dystonia, myoclonus, ataxia
Nutritional deficiencies	Vit B12, Vit B1, methyl malonic acid, homocystein, vit D	Need to consider it in any movement phenomenology
Strokes, tumors, structural abnormalities, hypo- or hyperglycemic injuries	Brain MRI	Dystonia, myoclonus, chorea, hemiballismus, ataxia
Lupus	ANA	Chorea, ataxia, tremor
Hypo- or hyperglycemia	Glucose levels	Dystonia, myoclonus, chorea, hemiballismus, ataxia
Dopamine-responsive dystonia (DRD)	Levodopa trial	DRD presents with dystonia or parkinsonism
Medication-induced MDS	Medication reconciliation and review	Need to consider it in any movement phenomenology
Recreational or drugs of abuse	Urine drug screen	Tremors, myoclonus, ataxia, chorea

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Bradykinesia is the hallmark of these conditions and presents with slowness of movement, decreased amplitude of repetitive movements (i.e., hypokinesia), and loss of normal movement (i.e., akinesia as in decreased facial expression). Parkinsonism can be caused by neurodegenerative conditions, medication side effects (like dopamine blockers), structural abnormalities, and other etiologies. The most common cause of parkinsonism is neurodegenerative [3] and medication-induced parkinsonism. The neurodegenerative categories include Synucleinopathies (Parkinson disease, multiple system atrophy (MSA), and dementia with Lewy bodies (DLB)), Tauopathies (progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD) and fronto-temporal dementias). Most of these conditions are classically called PD-Plus syndromes, as they present with additional signs that are not characteristic of PD. PD-PLUS syndromes do not respond long-term to dopaminergic agents and carry a much worse prognosis than PD, leading to mortality within 10–15 years.

Although PD can be seen in very young patients, the mean age of onset is 70 years and disease prevalence increases with age, with 1% at age 65 increasing to 4–5% by 85 years of age. Idiopathic Parkinson's disease (IPD) has a prevalence of about 0.3% in the general population with prevalence increasing to 4–5% by age 85. The pathological hallmark of IPD is accumulation of "Lewy bodies" inside the neurons, composed of alpha synuclein protein which spreads caudocranially [8].

Clinical Presentation

Parkinsonian patients usually present with symptoms related to their bradykinesia like slowness, decreased arm swing, lack of postural reflexes, small handwriting, soft speech, and slow gait with small steps. Rigidity and dystonia can present as stiffness, loss of dexterity, foot or toe curling, and abnormal postures. An acute or subacute onset is concerning for secondary etiologies, including dopamine-blockers use (up to five million Americans are exposed to antiemetic and antipsychotics) [10]. In addition to this, a response to levodopa and the absence of atypical symptoms are very suggestive of the disease [11]. Resting tremor is present in about two-thirds of patients with PD, but is less common in PD-PLUS syndromes [12]. Atypical symptoms such as early postural instability (within 3 years of onset), early gait freezing, hallucinations (not due to treatment), early cognitive impairment, medication sensitivity, and eye movement abnormalities suggest a diagnosis other than PD.

Physical Examination

Resting tremor is usually distal. PD patients might have a tremor during arm posture-holding (so-called re-emergent tremor). A useful feature to diagnose resting tremor is that its amplitude decreases or disappears as soon as the muscle involved with the tremor gets voluntarily contracted. Bradykinesia is characterized by decreased amplitude and speed of movements. Rigidity is an increase in tone irrespective of the speed of passive movement. A cog-wheel sign may be felt when tremor is associated with it. A search for atypical signs is very important as part of the examination (Table 3).

Differential Diagnosis

Drug-induced parkinsonism (DIP) is indistinguishable clinically from neurodegenerative parkinsonism. The best way of arriving to a diagnosis is through methodical withdrawal of possible causal medications. Common offenders include antipsychotics, antiemetics, calcium channel blockers, and drugs that deplete dopamine [13]. These drugs can also cause other movement disorders such as tardive dyskinesia, involuntary movement of the face causing twisting movements of the tongue or smacking of the

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Table 3 PD-PLUS signs and syndromes

Additional sign	Associated syndrome	Abnormal protein accumulated	Other names/notes
Upper motor neuron signs	Multiple systems atrophy	Alpha-synuclein	Striato-Nigral degeneration
Ataxia	Multiple systems atrophy (cerebellar subtype)	Alpha-synuclein	Olivo-ponto-cerebellar atrophy
Severe dysautonomia	Multiple systems atrophy (autonomic subtype)	Alpha-synuclein	Shy-dragger syndrome
Early dementia	Dementia with Lewy bodies	Alpha-synuclein	DLB
Abnormal extraocular movements, early gait dysfunction	Progressive supranuclear palsy	Tau	PSP
Hemi-dystonia, myoclonus, agraphiesthesia	Cortico-basal syndrome	Tau	Could be Corticobasal ganglionic degeneration, FTD and others
Early dementia, late parkinsonism	Alzheimer's	Amyloid, tau	About 30% of patients with AD have some parkinsonism

lips; it may cause abnormal movements of the limbs and can persist for years or becomes permanent after discontinuation of such medications [14].

Cerebrovascular disease can cause parkinsonism. Other rare but treatable etiologies include excess mineral deposition in the brain (Copper from Wilson's disease, Manganese), metabolic, autoimmune disorders, toxic chemicals (heavy metals, MPTP+, etc.). In addition, parkinsonism may also be seen in primary dementias such as Alzheimer's Disease, DLB, and Huntington Disease. Genetic causes include monogenic Parkinson diseases, autosomal dominant and recessive ataxias, and others.

However, the main differential diagnosis in PD is other neurodegenerative parkinsonism. There are many ways of classifying these conditions. A practical approach is to divide them PD (AKA typical PD or Idiopathic PD) and PD-PLUS syndromes (AKA atypical parkinsonism). PD main features are the parkinsonism triad. But in PD-PLUS, other additional signs are present on exam, which can help expand the differential diagnosis (Table 3). It is interesting to note that REM-sleep behavior disorders are tightly associated with alpha-synucleinopathies.

Diagnosis and Initial Work-up

The diagnosis of PD is clinical in nature. One reaches the diagnosis if a patient has a slowly progressive bradykinesia with either rigidity or resting tremor and lacks atypical signs and the syndrome cannot be explained by something else. Some treatable conditions could either cause parkinsonism or make it worse, including medication use, pregnancy, Wilson Disease, Thyroid abnormalities, liver, kidney or electrolyte/glucose abnormalities, and Vit B12, D, and E deficiencies (Table 2). Basic initial work-up to consider, pregnancy test, Ceruloplasmin, thyroid function, CMP, vitamin B12 level, MMA, homocysteine, folate, 25-OH Vit D3, Vit E. Environmental exposures, use of over-the-counter, herbal or illegal drugs should be ascertained. Structural imaging (usually with MRI of the Brain) could be considered in cases suspicious for MS, strokes, ataxia, primary, and metastatic tumors, in those with rapid or unusual progression, or with associated abnormal neurological examination. Functional imaging (like PET or SPECT) can help differentiate between Parkinson disease and Essential tremor. Referral to a Movement Disorders Center might be the most cost-effective measure when the diagnosis is not clear.

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An accurate medication list review as in any condition or chronic disease seen by Family Medicine physicians applies.

Treatment

Dopamine replacement can be useful in PD, RLS, and some dystonias. Other antiparkinsonian drugs target GABA-ergic, cholinergic, and other systems (Table 4).

Initial Monotherapy

Most commonly used drugs for initial monotherapy are levodopa (with carbidopa), Rasagiline, dopamine agonists, and occasionally anticholinergics. Rasagiline and Selegiline have modest benefits as monotherapy and therefore are usually used on mild to moderate severity cases. However, the mainstay treatment for PD is levodopa. There is no known long-term toxicity of using levodopa as initial therapy (ELLDOPA trial); [9] however, minimum effective doses should be used to avoid long-term complications (STRIDE-PD trial) [15]. Lack of enough peak benefit with levodopa is addressed by incremental doses. However, all medications in PD should start with a small dose and titrate up slowly over a matter of weeks. Patients with severe tremors respond best to levodopa, amantadine, and trihexyphenidyl.

Motor Fluctuations

Early in the course of the disease, when patients take levodopa, they see continual, long-lasting benefits, and usually not too many side effects. As the disease progresses, motor fluctuations occur including shortening of the duration of benefit of each levodopa dose and medication-induced dyskinesias. The shortening of the benefit of levodopa can be treated by providing the medication in shorter intervals or adding

Table 4 Common medications used in Parkinson disease

	MOA	Starting dose	Common SE	Warnings
Amantadine	Likely DA and glutamate	100 mg/day	Dizziness, insomnia	Death, suicidality, seizures, cardiac failure
Carbidopa/levodopa	Increase DA	25/100 mg 0.5 tabs TID, slow titration	Nausea, vomiting, dyskinesia	Suddenly stopping Sinemet can cause a severe withdrawal reaction
Entacapone	Reversible COMT inhibitor	200 mg TID with levodopa doses	Dyskinesia, drowsiness, and dizziness. Stool decoloration	Warning against concomitant use of COMT and MAO inhibitors
Pramipexole	Dopamine receptor agonist	0.125 mg TID (IR) or 0.375 mg/day (ER)	ICD, peripheral edema	Sleep attacks without warning. Hallucinations, orthostatic hypotension
Rasagiline or Selegiline	Irreversible MAO-B inhibitor	0.5–1 mg/day (Rasag) 5 mg BID (Seleg)	Headache, GI, depression, and dyskinesia	
Ropinirole	Dopamine receptor agonist	0.25 mg TID (IR); 2 mg/day (ER)	ICD, peripheral edema	Sleep attacks without warning. Hallucinations, orthostatic hypotension
Rotigotine	Dopamine receptor agonist	2 mg/day (patch only)	ASR, drowsiness and somnolence	Tachycardia, sleep attacks, orthostatism, ICD, rash

[a]PD drugs are pregnancy category C
[b]*IR* Immediate release, *ER* extended release, *ICD* Impulse Control Disorder

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entacapone or rasagiline. Dyskinesias require reduction of dopaminergic agents, or the addition of Amantadine.

Advanced and Surgical Treatment

There are currently two surgical procedures for PD: deep brain stimulation (DBS) surgery or DUOPA pump placement. DBS has become the standard of care in patients with poorly controlled symptoms not only for PD, but also for essential tremor and dystonia. The brain targets include thalamus (primarily for tremor any cause), subthalamic nucleus (PD) and globus pallidus (PD and dystonia) [13, 14]. DBS is highly effective in controlling symptoms and has been shown to significantly improve quality of like. With a low mortality and morbidity rate, it is considered very safe in surgical centers with enough experience. DBS usually does not lose its efficacy over the years and can be programmed so to adapt to new needs. DBS is also indicated in severe dyskinesias or medication-resistant parkinsonian tremors. DUOPA pump provides continuous levodopa gel infusion into the jejunum, eliminating the motor fluctuations and reducing dyskinesias.

Prognosis

PD has a good prognosis with an average life expectancy close to normal. Atypical Parkinsonisms have a shorter life expectancy of 10–15 years from diagnosis.

Referral and Education

Referral to a neurologist could be useful to handle cases with an unclear diagnosis, difficult-to-treat symptoms or to evaluate need for advanced therapies. Referral to a Movement Disorder specialist could be considered any time the diagnosis is uncertain, DBS or chemodenervation might be indicated, or the patient is responding poorly to medications. The American Parkinson Disease Association (APDA) and Parkinson Disease Foundation have chapters in every state and support groups in every major city. The APDA and the American Academy of Neurology (AAN) websites have many useful patient education resources [15].

Restless Leg Syndrome

Restless leg syndrome (RLS), also known as Willis-Ekbom disease, is characterized by an irresistible urge to move the legs to alleviate the presence of crawly sensations, commonly worse in the evening [4]. Prevalence in general population ranges from 7.2 to 11.5%; however, about 3% are severe enough to require treatment. The pathophysiology is unclear although is thought by experts that involves an abnormality of dopamine transmission, circadian physiology, thalamic function, other neurotransmitters such as GABA and glutamate, also reduced central iron sores.

Clinical Presentation

The clinical presentation follows the mnemonic URGE: **U**rge to move the legs (usually accompanied by creepy-crawly sensations), **R**est makes the symptoms worse, **G**etting up and moving makes symptoms better, **E**venings are worse. It has been associated with Periodic Limb Movements of Sleep (PLMS) and PD. When severe, symptoms can spread to the upper extremities [17].

Physical Examination

Clinical examination is usually normal. It is important to look for signs of secondary causes

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of RLS including anemia, pregnancy, renal failure, neuropathy, and parkinsonism.

Diagnosis

Restless legs syndrome (RLS) is a clinical diagnosis that is made by history and does not require additional testing, except for an assessment of iron stores, blood urea nitrogen and creatinine if uremia is suspected. Any potentially medications as a cause should be identified [18].

Differential Diagnosis

RLS symptoms can overlap with other conditions like akathisia (generalized restlessness and urge to move, commonly tardive or medication-induced), neuropathy, radiculopathy, myoclonus, leg pain, or positional discomfort.

Treatment

In RLS, Gabapentin and Pregabalin are effective first line therapy [19]. Due to long-term complications and significant side effects, it is suggested to avoid dopaminergic therapy as first line of treatment, although they are extremely effective (Table 4). A serum ferritin concentration lower than 50 mcg/L has been associated with increased severity of RLS and iron replacement is recommended if the fasting serum level is below 75 mcg/L [20].

Essential Tremors

Shaking is not an uncommon complaint at a family medicine office. One of the most common causes of tremor is *Essential Tremor (ET)*. ET affects 2–6% of the population (prevalence 305/100,000; incidence 23/100,000/yr). Onset peaks in early adulthood (third decade) and late adulthood (sixth decade). The pathophysiology of ET includes the possible involvement of the cerebellum, the Guillain-Mollaret triangle, and GABA-ergic mechanisms [5].

Differentiating Types of Tremors

Assessment of patients that presents to the office with shakings still depends upon the history and physical exam. There are many movement disorders phenomenologies that look like shaking, including tremor, myoclonus, dystonia, and tics. But tremor is an oscillatory, mostly rhythmic movement. Once the phenomenology is ascertained as a tremor, the next step is to determine which type of tremor. The scope of this chapter constrains us to review only a few of the many types of tremors.

Resting tremor is one which amplitude decreases or disappears as soon as the muscles involved with the tremor get voluntarily contracted. Therefore, it is predominantly present during rest. This tremor might also appear after the patient has been holding arms up in front for a while (usually in the wrist or fingers), the so-called re-emergent tremor. Again, re-emergent tremor will usually disappear by contracting the involved muscles, helping differentiation from other postural tremors.

Action/kinetic tremors are those that appear or which amplitude increases as soon as the muscles involved with the tremor get voluntarily contracted.

Intention tremor is a posture-kinetic tremor which amplitude increases with target-directed movements (e.g., while comparing the tremor during finger-to-nose-finger maneuver versus just holding the arms straight). Intention tremor is regarded as a sign of disturbed function of the cerebellum and its pathways.

Posture-specific or task-specific tremor is commonly due to dystonia. Examples include the tremor present during flexion of a limb but not during extension; or the *intermittent, jerky, irregular, arrhythmic* head tremor of patients with cervical dystonia. Particular features that differentiate dystonic tremor from other tremors include the presence of abnormal posturing, muscle hypertrophy, null point (a place in the range of

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motion of the joint involved where tremor amplitude significantly decreases), and sensory tricks (AKA geste antagoniste, a sensory stimulus like touching the area can improve the dystonic tremor). Also to this category appertain the task specific tremors (e.g., those present only during writing or while playing an instrument) [2].

Clinical Presentation

The diagnosis is clinical. Essential tremor is a familial action hand tremor. It presents as a gradual onset of postural and action tremor in both hands and forearms, worse with stress or fatigue. Two thirds of patients notice that the tremor improves with alcohol. ET worsens over years and can involve head, voice, jaw, trunk, and legs [5]. Although ET patients can have shaking in other body parts, it would be very rare to have ET without hand tremors.

ET tremor is regular and rhythmic (jerky and irregular suggest dystonia or myoclonus), distal and does go away with true rest (tremor at rest suggests PD, dystonia or myoclonus). Head tremor can be vertical or horizontal, and voice tremor is rhythmic and regular [5].

Differential Diagnosis

Essential tremor needs to be differentiated from resting, dystonic, ataxic, physiologic, rubral, myoclonic, and medication-induced action tremors. The most common medications that can cause tremor include antidepressants, adrenergic agonists, antiarrhythmics, benzodiazepines, analgesics, anesthetic, antiepileptics, and others. When patients have action tremors with other associated signs like ataxia or dystonia, this is called ET-Plus.

Treatment and Prognosis

Drugs with most robust evidence for treatment include propranolol, primidone, and topiramate. Although propranolol is the usual first trial, drug choice is based on side effect profile (Table 5). ET has a normal life expectancy with some gradual

Table 5 Commonly used medications in various MDS

Drug and main indication	Mechanism of action	Starting dose	Common side effects	Warnings (including black box)
Clonazepam (dystonia)	GABA agonist	0.5 mg QHS	Drowsiness, ataxia	Cognitive impairment, suicidality, fetal malformation
Gabapentin (RLS)	Voltage gated Ca^{+} channel	100–300 mg TID	Somnolence, cognitive SE, dizziness	Effects on driving, sedation, suicidal behavior or ideation, multiorgan hypersensitivity
Pregabalin (RLS)	As above	50 mg BID	Blurred vision, weight gain	As above and angioedema, PR interval prolongation, decreased platelet count
Primidone (ET)	GABA agonist	50 mg QHS	Ataxia, Vertigo	CI: Porphyria Suicidal ideation or behavior
Propranalol (ET, Akathisia)	Beta adrenergic blocker	80 mg daily (XL)	Fatigue, SOB dizziness, depression	WPW, cardiac failure, bradycardia, bronchospasm, hypoglycemia, erectile dysfx
Topiramate (ET)	GABA and sodium channel	Titration from 25 mg BID	Cognitive dysfunction, fatigue	Glaucoma, visual field defects, oligohydrosis and hyperthermia, Met. Acidosis
Trihexy-phenidyl (dystonia, PD)	M1 Ach R antagonist	2 mg q day	Blurred vision Dizziness	Glaucoma, bradycardia, oligohydrosis

RLS restless leg syndrome, *ET* essential tremor, *BID* twice daily, *QHS* once every night, *Ach R* Acetylcholine receptor, *WPW* wolf Parkinson white syndrome

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worsening of symptoms. However, many patients develop significant difficulties in activities of daily living, and tremor can affect professional performance.

Dystonia

Dystonia is an involuntary, sustained contraction of muscles resulting in abnormal postures or jerky tremor. Dystonia can be focal or generalized and is caused my many conditions. US incidence is 4.47/10 [5]. Its prevalence has been likely underestimated to be $16.43/10^5$ [7, 8]. Most common locations for primary etiologies are periocular (blepharospasm), cervical, and laryngeal dystonia [21].

Clinical Presentation

Presents as focal (most common neck and eyes), segmental, hemi-dystonia, or generalized. It is usually painless (except cervical dystonia) and its severity fluctuates based on stress, fatigue, and activity [21, 22]. It is important to document areas of involvement, posturing, effect of activity and distraction, presence of tremors, and associated disorders (for example PD). Blepharospasm is the most common focal dystonia, causing excessive blinking, squinting, and difficulty keeping eyes open. Cervical dystonia causes a combination of torticollis (chin to one side), anterocollis (chin pulled down), retrocollis (chin pulled up), and laterocollis (head to one side) and is commonly associated with a jerky head tremor.

Differential Diagnosis

Dystonia needs to be differentiated from ET (usually have hand tremors), ataxic tremor (other signs of ataxia), neck pain from orthopedic causes (abnormal imaging, cervical radiculopathy), and Parkinson Disease (which may or may not be present with it).

Treatment

Most effective oral drugs include Clonazepam, Trihexyphenidyl, and Baclofen. Treatment of choice for most focal dystonias is chemodenervation with botulinum toxin injections, which act by blocking the release of Acetylcholine at the neuro-muscular junction. Chemodenervation is highly effective, with sustained, safe benefit expected through many years of therapy [6] (see Table 5).

Ataxia

Ataxia is the type of clumsiness that is produced by dysfunction of the cerebellum and its pathways [9]. Mild ataxia is part of many movement disorders, and also ataxic syndromes tend to have a myriad of other movement phenomenologies [1, 9]. Therefore, the prevalence of ataxia is likely underestimated. Perhaps one of the most common causes of ataxia is medication induced. The list of the many drugs implicated includes some of the most common medications used in practice, including antidepressants, antiarrhythmics, adrenergic agonists, benzodiazepines, analgesics, anesthetic, antiepileptics, and others.

Clinical Presentation

The usual syndrome is such of hand clumsiness, abnormal or unstable gait, and dysarthria. The examination in ataxia can reflect any of the following abnormalities:

- Asynergia: decomposition of movements. Instead of the normal smooth performance, there is breakdown of the movement, rendering it irregular.
- Dysdiadochokinesia: a manifestation of asynergia is the break-up and irregularity seen while performing rapid alternating movements.
- Dysmetria: the misjudging of distance. Dysmetria includes hypermetria (overshooting), hypometria (undershooting), and loss of

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check (inability to stop a ballistic movement right on target).
- Intention tremor (see the Tremor Chapter): Tremor that is characteristically worse during target-directed movements (in comparison with that of posture holding or other actions).
- Hypotonia: decrease tone is common in cerebellar syndromes.
- Rebound: sudden displacement of a limb that is holding a posture produces excessive overcorrection).
- Gait/truncal ataxia: characterized by irregular stepping (worse with tip-toe or heels ambulation), increased lateral sway (not a straight line of ambulation), unstable turns, inability to walk on tandem. Wide-based ambulation, spontaneous retropulsion, and true postural instability are more advanced signs of ataxia.
- Ocular ataxia: characterized mostly by dysmetric ocular saccades, tends to be associated with nystagmus. Patients might experience diplopia.
- Ataxic dysarthria: global dysarthria but with a very strong component of lingual dysarthria, frequent volume changes (usually with overall hypophonia), scanning speech.

Diagnosis

The diagnosis of ataxia is clinical. But the diagnostic work-up to find the etiology of the ataxia is complex and long. Diagnoses not to miss in clinical practice are: medication-induced, paraneoplastic syndromes, Wilson disease, thyroid abnormalities, metabolic abnormalities (liver, kidney, or electrolyte/glucose), Vit B12, D, and E deficiencies, stroke, multiple sclerosis, hydrocephalus, and tumors (medulloblastoma, astrocytoma, ependymoma, metastasis, and others). Environmental exposures, use of over-the-counter, herbal or illegal drugs should be ascertained. Paraneoplastic ataxias often precede structural symptoms from the primary tumor and other usual cancer clues, and therefore, their diagnosis has important implications and requires checking the test. In fact, currently about a third of all cancers are been diagnosed as a paraneoplastic syndrome first, bringing an early recognition to those cancers and possible prognostic implications.

Structural myelopathy is one of the most common causes of truncal ataxia, and early diagnosis avoids progression. This presents as gait abnormality, urinary urgency, and upper motor neuron signs.

In children, important etiologies for acute ataxia include intoxication, acephalalgic (no headache) migraine, and cerebellitis (usually Varicella-Zoster Virus). Chronic ataxias would point to congenital defects of metabolism and genetic etiologies.

Basic initial work-up to consider: peripheral smear (looking for acanthocytes), Ceruloplasmin, Thyroid function, CMP, RPR, Vitamin B12 level, MMA, Homocysteine, folate, 25-OH Vit D3, Vit E, antigliadin antibody, urine drug screen, paraneoplastic panel. Consider heavy metals testing if other tests are negative. Ataxic patients usually require Brain and Spinal Cord MRI imaging (CT is not enough), unless etiology has been identified.

Other Clinical Diagnostic Considerations

If the basic initial work-up (above) is unrevealing, the next phase of the work-up might be better performed at a Movement Disorders Center, as there are hundreds of possible tests. Also, proper genetic counseling is required before proceeding with many of the tests.

Sporadic ataxias: If initial work-up is negative (see above), other etiologies include Multiple Systems Atrophy, Celiac Disease, Creutzfeldt-Jacob disease, genetic ataxias (like Friedrich Ataxia, SCA 2, 3, and 6), and paraneoplastic syndromes (false negative panel tests are expected). One of the most common causes of ataxia is alcohol abuse. Cerebellar degeneration due to alcohol is always a consideration. But a particular alcohol

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syndrome, the dorsal vermial atrophy, is associated with severe truncal ataxia.

Genetic Ataxias: A good source of genetic ataxia information includes the Online mendelian inheritance in Man (OMIM) and the Washington University in St. Louis Neuromuscular website [23]. Special mention is needed for a relatively new, highly prevalent, commonly undiagnosed disease called Fragile X-associated Tremor and Ataxia Syndrome (FXTAS) [22]. This syndrome is seen in those carriers of the Fragile X premutation and might also have parkinsonism and dementia. MRI of the brain is abnormal in 2/3 of the cases to include the MCP or the splenium signs.

Dominant Ataxias include the SCA's (Autosomal Dominant Spino-Cerebellar Ataxias), DRPLA, and the episodic ataxias. There are more than 25 SCA's and their differentiation is difficult, rendering the SCA panel genetic testing an expensive test to consider. Recessive Ataxias include Friedreich Ataxia (FA), abetalipoproteinemia, Ataxia-Telangiectasia syndrome, and the treatable, isolated Vitamin E deficiency (TTP1 gene mutation). FA is the most common one and presents with upper motor neuron signs, neuropathy, diabetes, and cardiomyopathy. It is caused by an expanded GAA repeat on the Frataxin gene.

Treatment

The field on curative options for ataxic syndromes is expanding rapidly, including antisense oligonucleotides, gene-silencing, and other innovations. However, the treatment of most ataxic patients is supportive. Occupational therapy (OT) and physical therapy (PT) are extremely helpful in keeping patients independent. Gait and balance therapy can lead to decrease falls and improve walking. Other symptomatic management options are largely dependent on comorbid aspects of the primary cerebellar process. For example, patients with marked spasticity may benefit from oral drugs and chemodenervation.

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Disorders of the Peripheral Nervous System

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Kirsten Vitrikas and Norman Hurst

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Background

Disorders of the peripheral nervous system are caused by a variety of diseases, toxins, trauma, and metabolic causes. Neuropathies are estimated to affect 7–10% of the population with the incidence being higher in older individuals [1]. Depending on the cause a single or multiple nerves may be involved. The most common causes of polyneuropathy are diabetes, alcoholism, fatty liver disease, and malignancy.

In axonal disease typically the more distal ends of the nerves are affected first resulting in the "stocking and glove" distribution seen in diabetic neuropathy. This type of damage will also result in loss of distal reflexes (i.e., ankle jerk) with preserved reflexes elsewhere. Demyelinating neuropathies often have proximal weakness with generalized loss of reflexes. Pain, loss of temperature sensation, and autonomic features suggest involvement of small nerve fibers. Autonomic features include light intolerance (pupillary), postural hypotension (cardiovascular), nocturnal diarrhea (gastrointestinal), impaired sweating (sweat gland), and bladder dysfunction. These symptoms may occur as part of diabetic neuropathy or as a sign of more systemic nerve involvement such as with amyloidosis or autoimmune conditions. Many diseases have mixed involvement of both sensory and motor symptoms.

Compressive neuropathies often result from overuse or mechanical problems. Presentation is more common in the later decades. For all compressive neuropathies except carpal tunnel, initial presentation is usually at ages 55–64 [2]. Carpal tunnel is more likely to present initially in women aged 45–54 years, and radial nerve palsy is more common in men aged 75–84 years [2]. Prevalence rates from a UK study are shown in Table 1.

The duration of development may help provide clues as to the etiology and is divided into categories: acute (<4 weeks), subacute (1–3 months), and chronic (>3 months). Neuropathies that occur acutely tend to be related to vasculitis or Guillain-Barre syndrome [3].

Evaluation

A thorough history and physical should be performed looking for underlying causes and clues to systemic disease. Patients will typically experience burning or electrical like sensations, paresthesias, weakness, or pain from non-painful stimuli like light touch. They may also suffer from sleep disturbances, anxiety, and mood disorders.

Table 1 Prevalence of compressive neuropathies

Type	Prevalence	Female/male
Carpal tunnel	2.78%	3–1
Morton's neuralgia	1.27	2–1
Ulnar neuropathy	0.4	1–1.3
Meralgia paresthetica	0.22	1–1
Radial neuropathy	0.045	1–2

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The patient should be questioned about toxin exposures including occupational exposures, prescribed medications, and chemotherapy treatments in addition to nutrition. Careful examination of the neurologic system should involve testing of sensory function including vibration, proprioception, temperature, and pinprick in addition to reflexes. Specific testing may be performed for mononeuropathies such as carpal tunnel syndrome (Tinel's, Phalen's).

Initial laboratory testing to determine causes should include a complete blood count, comprehensive metabolic profile, erythrocyte sedimentation rate, fasting blood glucose or hemoglobin A1C, vitamin B_{12}, and thyroid-stimulating hormone levels [3]. Additional testing based on clinical suspicion may include human immunodeficiency virus (HIV) antibodies, Lyme antibodies, rapid plasma reagin (syphilis), urine and serum protein electrophoresis (paraproteinemias), angiotensin-converting enzyme levels (sarcoidosis), and antinuclear antibodies (vasculitis). In at least 15% of cases, a cause may not be determined with this initial testing [3]. The etiology in these cases is often autoimmune or hereditary [3]. Lumbar puncture and cerebrospinal fluid (CSF) analysis may also be helpful in diagnosis of Guillain-Barre syndrome or chronic inflammatory demyelinating neuropathy, which usually has notably elevated protein levels.

Electrodiagnostic testing consisting of nerve conduction studies and electromyography (EMG) should be considered if the diagnosis remains unclear after initial evaluation [3]. These studies can help determine if the damage to the nerve is axonal, demyelinating, or mixed. Normal studies decrease the likelihood of the peripheral neuropathy as the cause of symptoms. These studies are not as sensitive for neuropathies of small nerve fibers (pain, temperature, or autonomic functions).

Nerve biopsy is considered when the diagnosis still remains uncertain or when confirmation is needed prior to initiating aggressive treatment (e.g., vasculitis which may require immunosuppressive medications). Sural and superficial peroneal nerves are preferred for biopsy. Epidermal skin biopsy may also be performed in patients who are suspected to have disease of their small nerve fibers [3].

Cranial Neuropathies

Bell's Palsy

Bell's palsy is an acute unilateral facial nerve paralysis of unknown etiology. Patients usually describe an acute onset of unilateral facial weakness. They may have an associated earache in addition to numbness in the distribution of the nerve. Both upper and lower parts of the face are affected which distinguishes this from a central lesion in which only the lower portion of the face is paralyzed. This condition affects 11–40 persons per 100,000 with peak incidence between the ages of 15 and 50 years [4]. Groups at higher risk include pregnant women, diabetics, the elderly, and patients with hypothyroidism [4]. The cause is unknown, though there is evidence that a reactivation of herpes virus, either herpes simplex 1 (HSV-1) or herpes zoster (HZV), is involved. Several other infectious causes have been implicated in addition to autoimmune disease (Hashimoto's), ischemia, and familial syndromes [4]. The symptoms result from inflammation and edema of the facial nerve. Most patients recover within weeks to months.

Laboratory and imaging studies are not routinely needed. They are only recommended when there is concern for Lyme disease, recurrence of symptoms, or no improvement after 3 weeks of treatment [5]. Even without treatment approximately 70% of patients with complete paralysis will recover within 6 months. A Cochrane review showed that corticosteroids had significant benefit in the treatment with faster recovery and improved nerve function when started within 72 h of symptom onset [6]. Antivirals in combination with corticosteroids may reduce the incidence of long-term sequalae, such as excessive tearing or facial spasms [7]. Care should be taken to protect the cornea due to improper lid closure caused by the disease. This may be done with lubricating drops or eye ointment during sleep. In addition,

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providers may need to provide psychological support to patients with this disfiguring condition [4, 5]. Surgical decompression may be considered for severe cases (complete paralysis or absent electromyographic activity). [8].

Trigeminal Neuralgia

Trigeminal neuralgia (tic douloureux) is defined as sudden, usually unilateral brief stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve by the International Classification of Headache Disorders and further classifies the condition as classic (idiopathic) and secondary (associated with a structural abnormality) [9]. Incidence is reported as 4.3–27 cases per 100,000 people per year. The most common cause is compression of the nerve by a blood vessel. Routine neuroimaging may identify a cause in up to 15% of patients [10]. Patients with bilateral symptoms, younger age, and the presence of trigeminal sensory deficits are more likely to have secondary trigeminal neuralgia, though there is significant overlap with the classic form [10]. Secondary disease is often associated with multiple sclerosis. Carbamazepine has been shown effective for treatment in doses ranging from 300 to 2400 mg per day, as has oxcarbazepine at 600–1800 mg per day. Baclofen, lamotrigine, and pimozide have shown effectiveness in single trials [10]. When symptoms are refractory to treatment with medications, surgical therapy may be considered.

Mononeuropathies

Carpal Tunnel Syndrome

Carpal tunnel syndrome arises from compression of the median nerve. Patients complain of paresthesias, pain, and numbness in the distribution of the median nerve, which includes the thumb, index, and middle fingers and the radial half of the ring finger on the palmar side. It presents more commonly in women. Risk factors include obesity, diabetes, pregnancy, menopause, ovariectomy, and hysterectomy [11]. The condition can be caused by repetitive strain injury or other conditions causing edema and inflammation of the synovial sheath. Examination may reveal thenar atrophy and reproduction of symptoms with provocative testing such as Tinel's or Phalen's test. The diagnosis is usually made clinically. One may consider nerve conduction studies or ultrasound when the diagnosis is in question, surgery is planned, or as a predictor of symptom severity and functional status [12].Treatment is based on severity of symptoms and physical limitations [11]. In pregnant women, the symptoms usually resolve after birth. Conservative treatment may consist of behavior modification, analgesics, splinting, physical and occupational therapy, oral corticosteroids, and ultrasound [13]. Additional treatment with local steroid injection may be attempted when conservative measures fail. In patients who fail conservative treatment or have evidence of median nerve denervation, surgery should be considered [13].

Cubital Tunnel Syndrome

Cubital tunnel syndrome is the second most common entrapment neuropathy after carpal tunnel syndrome. Compression of the ulnar nerve causes pain or paresthesias in its distribution involving the fourth and fifth finger and the medial aspect of the elbow. Conservative therapy consists of splinting and activity modification. Steroid injections do not seem to offer benefit over splinting. Surgery may be considered for persistent symptoms; however, there is controversy as to which patients benefit from surgery [14].

Radial Neuropathies

The characteristic feature of radial tunnel syndrome is pain over the lateral proximal forearm with little or no motor weakness. It is difficult to differentiate this syndrome from lateral epicondylitis due to location of the pain; however, the pain from radial tunnel syndrome should be 3–4 cm distal to the lateral epicondyle [15]. Posterior

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interosseous nerve syndrome results from compression of the same nerve; however, it results in loss of motor function with patients complaining of motor weakness in the first three fingers. The function of the wrist should be preserved in these cases [15]. Initial therapy for both of these conditions should be rest, activity modification, splinting, and anti-inflammatory medications. Particularly for posterior interosseous nerve syndrome, one should consider removal of any masses such as lipomas or ganglions that are causative. Injection of steroids may serve therapeutic and diagnostic purposes for radial tunnel syndrome. If there is no improvement after 3 months, surgery should be considered for both conditions [15].

Posture-induced radial neuropathy, popularly known as Saturday night palsy or sleep paralysis, is a result of prolonged compression of the radial nerve and causes a wrist-drop. The most common cause is due to sleeping with the arm over the back of a chair particularly while drunk. Symptoms usually resolve with conservative treatment of splinting and avoidance of provocative activities. Patients with denervation findings on needle EMG and severe initial weakness have a poorer prognosis for long-term recovery [16, 17].

Lumbosacral Neuropathies

Trauma involving the lumbosacral plexus is much less common than that of the brachial plexus; lumbosacral neuropathy may occur perioperatively (especially with lithotomy positioning), with pregnancy and childbirth, or from compression by aortic aneurysms or tumors. Vascular lesions associated with diabetes may produce a proximal multiple mononeuropathy of the plexus.

The clinically important branches of the upper, lumbar portion of the plexus include the lateral femoral cutaneous nerve, obturator nerve, and femoral nerve. The lower, sacral portion of the plexus gives rise to the inferior and superior gluteal nerves and the sciatic nerve; the sciatic nerve branches form the common peroneal and tibial nerves.

Meralgia Paresthetica

Compression neuropathy of the lateral femoral cutaneous nerve of the thigh may occur where it passes underneath the inguinal ligament or where it pierces the fascia lata. It occurs most frequently in overweight individuals or in diabetics. Compression may also occur as the result of a tight belt compressing the nerve as it passes over the iliac crest or from prolonged extension such as may happen during surgery. Patients experience increasingly severe numbness, pain, and paresthesias, as well as decreased sensation of the anterolateral thigh; there is no weakness. Tests such as the pelvic compression test and Tinel's sign performed over the nerve as it exits the inguinal ligament region may help solidify the diagnosis. Treatment is generally conservative with avoidance of compression activities, anti-inflammatory medications, and physical therapy [18].

Femoral Neuropathy

The femoral nerve mediates extension of the leg at the knee through innervation of the quadriceps muscle. Its sensory distribution includes the anteromedial aspect of the thigh and the medial aspect of the lower leg and foot. The femoral nerve is commonly affected by diabetic vascular mononeuropathy, surgical positioning, and inguinal hernia, or tumor involving the lumbar plexus may also compress it.

Sciatic Neuropathy

The sciatic nerve arises from the sacral portion of the plexus. It leaves the pelvis through the sciatic notch and passes down the posterior thigh, where it divides into the tibial and peroneal nerves at the level of the popliteal fossa. The sciatic nerve innervates the extensors of the thigh, the hamstrings, and all of the muscles of the lower leg and foot; it also supplies sensation to the perineum, posterior thigh, lateral calf, and foot. Pain and weakness in the distribution of the sciatic nerve are most commonly the result of lumbar disk herniation, although fractures of the pelvis or femur, gunshot wounds to the buttock and thigh, or pelvic tumors may damage the sciatic nerve itself.

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Peroneal Neuropathy

The common peroneal nerve mediates dorsiflexion and eversion of the foot and supplies sensation to the dorsum of the foot and ankle. It is particularly prone to compression at the level of the fibular head, whether due to trauma, sitting cross-legged, improperly applied stirrups at the time of delivery, or an ill-fitting cast. Diabetic, vasculitic, and hereditary neuropathies may also affect the peroneal nerve. Treatment consists of conservative management with activity modification and bracing. Surgical treatment can be considered for severe cases, compressive masses, or lack of response to conservative treatment. [19].

Interdigital Neuralgia

Entrapment neuropathy of the interdigital nerve is a common cause of foot pain. Morton's neuroma, a benign swelling of the nerve, is usually responsible. Unlike metatarsalgia, there is palpable tenderness between the metatarsal heads in the second or third web spaces. Runners, ballet dancers, and women who wear tight shoes and high heels are particularly prone to the development of a neuroma. Conservative measures such as steroid injection and mobilization have shown some benefit. [20] Surgical resection is often necessary.[21].

Polyneuropathies

Thoracic Outlet Syndrome

Thoracic outlet syndrome (TOS) encompasses several clinical entities. Currently it is categorized as vascular (arterial and venous), neurologic (true/classic and disputed), and neurovascular/combined (traumatic and disputed). Neurologic accounts for the majority of cases. This type most commonly affects the brachial plexus due to either direct trauma or repetitive stress injury. There is a female predominance. True neurologic TOS is a unilateral disorder affecting mainly women due to fibrous bands extending from a cervical rib causing stretching and compression of the proximal lower trunk of the brachial plexus. Traumatic TOS is most commonly caused by a midshaft displaced clavicle fracture.

Patients present with hand weakness, atrophy, and loss of dexterity. They may also have a preceding history of intermittent medial upper extremity and forearm myalgias and paresthesias that are exacerbated by shoulder and neck movement. Depending on the rami, affected patients will report pain from the head, neck, thorax, shoulder (upper plexus; C5–C6) or neck, medial arm, forearm, and fourth and fifth digits (lower plexus; C8–T1). Motor function is affected preferentially with patchy sensory deficits. There may also be vascular symptoms along the forearm and medial arm. Provocative tests such as Adson maneuver, Halstead test, Roos test, and Wright maneuver may be used to potentiate symptoms. Radiographs may be helpful in revealing the presence of a cervical rib or clavicle fractures.

True neurologic TOS should be treated surgically to disrupt the fibrous band and prevent further nerve damage. Disputed TOS is initially treated medically using multiple modalities that include rest, activity restrictions, analgesics, anti-inflammatory medications, and muscle relaxants. Physical therapy modalities are numerous. Surgical therapy for disputed TOS can be considered after 3 months of attempted medical therapy [22].

Brachial Plexus

Brachial plexopathies may be due to any trauma involving the axilla or causing a violent increase in the angle between the shoulder and head, producing stretching or even tearing of various plexus elements. This injury, the cause of the "burner" or "stinger" syndrome seen in football players, results in temporary numbness, paresthesias, and diffuse weakness of the arm and shoulder [23]. Direct extension of apical lung tumors or breast cancer may cause similar symptoms. It is often difficult to distinguish between metastatic brachial plexopathy and late-onset impairment caused by radiation therapy.

Acute idiopathic brachial neuropathy also known as Parsonage-Turner syndrome or neuralgic amyotrophy is a rare disorder characterized by

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rapidly progressive pain of neck and shoulder followed by progressive weakness and hyporeflexia. The etiology is uncertain, but it has been reported in association with surgery, infections, trauma, and vaccination. The condition is generally self-limited with the pain lasting 1–2 weeks. The weakness may develop days to weeks after the onset of other symptoms. Treatment involves control of pain symptoms with anti-inflammatory medications, opiates, and neuroleptics. There may be some role for oral steroids, but further studies are needed to establish efficacy. Once the initial pain has abated, physical therapy plays a role in strengthening the affected muscles; timing depends on the level of denervation of the muscles [24].

Lumbosacral Plexus

Lumbosacral plexitis is a rare condition that presents with acute onset of severe lower extremity pain followed by wasting and weakness of leg muscles. It is usually unilateral, though many patients may develop bilateral symptoms. Sensory loss is variable. Patients typically have weight loss and elevated erythrocyte sedimentation rates. Mass lesions and trauma should be excluded as causes. One must also look for mimics such as diabetes or Lyme disease. Peak incidence is in children and age 40–60 years. There may be an antecedent history of viral illness or vaccination particularly in children. It is considered an autoimmune disorder with biopsies typically showing microvasculitis. This condition can often be mistaken for lumbar radiculopathy because patients will show abnormalities on magnetic resonance imaging of the spine. Those with milder disease should be offered supportive care and physical therapy. For more severe cases, immunomodulatory therapy may be considered. However, due the rarity of the condition, there is little data to support a specific regimen. Patients with milder disease will resolve over weeks to months with pain improving before the weakness. Some will go on to develop a relapse with progressive disability [25].

Infectious Neuropathies

Postherpetic Neuralgia

Herpes zoster results from reactivation of dormant varicella-zoster virus. Patients develop a vesicular rash and pain in a single dermatome. The postherpetic pain results from direct damage to the peripheral nerve. Classically the condition is defined as pain persisting at least 90 days after the appearance of the rash. Approximately 20% of patients report some pain at 3 months after onset and 15% report pain at 2 years. Risk factors for development of the condition include older age and greater severity of the prodrome, rash, and pain during the acute phase.

The only effective method of prevention is with vaccination. A live attenuated and subunit adjuvanted herpes-zoster vaccines are available for persons 50 years of age and older and have been shown to reduce the incidence of herpes zoster by 51% and incidence of postherpetic neuralgia by 66% or more. [26, 27] While the use of antiviral drugs has been shown to reduce the severity of acute pain and rash in addition to hastening rash resolution with herpes zoster, the trials did not assess the subsequent incidence of postherpetic neuralgia. Addition of steroids to antiviral treatment has not been shown to reduce the incidence of neuralgia.

Topical therapy is considered first line for mild pain, though evidence is equivocal as to its benefit. Lidocaine patches (Lidoderm) 5% and capsaicin cream 0.075% (off-label use) or patch (Qutenza) 8% may prove helpful. Side effects are minimal and mainly related to local reactions. Several studies have shown benefit with use of tricyclic antidepressants (off-label use), gabapentin, and pregabalin [28, 29].

Leprosy

While uncommon in industrialized countries, leprosy remains one of the most common treatable causes of peripheral neuropathy worldwide, particularly in tropical countries. Typically patients present with mononeuritis or mononeuritis

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multiplex. It causes a predominantly axonal neuropathy with more severe symptoms in the lower limbs. There is a subtype of leprosy in which patients have purely neural symptoms without the classic skin lesions. Diagnosis can be difficult in these patients as it predominantly affects small nerve fibers. Biopsy will assist in establishing the diagnosis [30].

Hepatitis C

Hepatitis C may cause several different patterns of peripheral neuropathy: polyneuropathy, mononeuropathy or multiple mononeuropathies, cranial neuropathy, or a combination of polyneuropathy and cranial neuropathy. Biopsies show inflammatory vascular lesions and axonal degeneration supporting an ischemic mechanism rather than a direct role of the virus [30].

Human Immunodeficiency Virus (HIV) Infection

Neuropathy occurs in approximately 35% of acquired immunodeficiency syndrome (AIDS) cases. The main patterns are multiple neuropathy, acute or chronic inflammatory neuropathy, polyneuropathy, and distal symmetric neuropathy (DSN). Age, use of antiretroviral medications, severity of HIV infection, diabetes, alcohol use, and race are associated with development of distal symmetric neuropathy in particular. The antiretroviral drugs stavudine, didanosine, and zalcitabine have been implicated as causative in some patients. Differentiation of these drugs versus the virus as the cause can be made by withdrawing the potentially offending agent with improvement of symptoms [30]. Early initiation of highly active antiretroviral therapy significantly lowers the risk of developing distal symmetric neuropathy.

Lyme Disease

In the acute phase, patients with Lyme disease frequently present with subacute cranial neuropathies particularly Bell's palsy. Late disease symptoms are more likely to be symmetric sensory polyneuropathies. In areas with endemic Lyme, many authorities recommend checking titers as a potentially treatable cause of peripheral neuropathies. Treatment is aimed at the underlying infection with doxycycline 100 mg orally twice daily for 14 days. Parenteral regimens may be considered for treatment failure or severe disease [31].

Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barre Syndrome)

Incidence of Guillain-Barre syndrome (GBS) is 1–2 cases per 100,000. Patients present with acute onset of symmetric ascending motor weakness, although a substantial portion of patients have sensory symptoms. Pain presents in 50–60% and will sometimes precede the weakness. Patients have decreased or absent deep tendon reflexes. Diagnosis is made mainly on clinical presentation [32], though cerebrospinal fluid examination and nerve conduction studies may aid in diagnosis in atypical cases. There is suggestion that host factors play a role, though no definitive genetic link has yet been found. *Campylobacter jejuni* gastroenteritis is the most frequently associated antecedent infection though several other infectious etiologies and vaccines have been implicated.

All patients should be hospitalized to monitor respiratory status, as 20–30% will progress to respiratory failure, and neurological consultation obtained. Treatment with plasmapheresis or intravenous immunoglobulin (IVIG) should be initiated early in the disease course. These treatments are felt to be equally efficacious [33, 34]. Supportive care with invasive ventilation may be necessary. Gabapentin and carbamazepine have shown some promise in treating pain associated with GBS [35]. Intensive rehabilitation produces greater functional improvement and reduces disability in the later stages of recovery [32]. Full recovery can take months to years [36].

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Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare acquired immune-mediated progressive or relapsing disorder causing peripheral neuropathic disease of duration more than 2 months. Incidence is reported to be 0.67–10.3 per 100,000 worldwide with a slight male predominance. Clinically patients present with proximal and distal weakness, sensory involvement, and areflexia. Lab testing may be positive for paraproteins such as anti-myelin-associated glycoprotein and anti-ganglioside antibodies. Cerebrospinal fluid protein levels are usually elevated. Nerve conduction studies help with diagnosis as does nerve ultrasound and MRI. There are now recognized to be atypical subtypes of the disease that respond differently to treatments [37]. IVIG and corticosteroids are considered first-line treatment. Small studies have shown some benefit of other immunomodulating agents [38].

Metabolic Neuropathies

Diabetic Neuropathy

Diabetic neuropathy is the most common polyneuropathy encountered by family physicians. Neuropathy may occasionally be the presenting feature of diabetes, but more commonly it is related to increasing duration and severity of the disease. Therefore good glycemic control is essential in the prevention or delay of this condition.

Diabetic neuropathies encompass the spectrum of peripheral nerve disorders. Classically, patients experience distal symmetric polyneuropathy with predominantly sensory involvement and mild motor signs (stocking and glove pattern). Damage to the small nerve fibers results in sensations of burning or lancing pains particularly on the soles of the feet. Decrease in sensation may be confirmed with testing using a 10 g monofilament. Damage to the large nerve fibers leads to decreased position sense and may progress to sensory ataxia and arthropathy (Charcot joint).

Patients with diabetes also experience a higher frequency of compression and entrapment mononeuropathies than those without the disease. Diabetic amyotrophy is a multiple mononeuropathy involving the lumbosacral plexus or motor fibers of the lower extremity as described above (lumbosacral plexopathies). This condition is felt to be partly ischemic in nature though evidence also suggests immune-mediated etiology.

Some diabetic patients will present with purely autonomic signs and symptoms. Postural hypotension is common, but gastrointestinal (diabetic gastroparesis, intestinal hypomotility, and constipation or diarrhea) and genitourinary (impotence, neurogenic bladder) symptoms may also occur.

For treatment of painful diabetic neuropathy, only duloxetine and pregabalin are FDA approved; however, studies support use of numerous other agents in the treatment of this condition. Venlafaxine, tricyclic antidepressants, gabapentin, valproate, and botulinum toxin are other options for treatment. Opioids and tramadol can be considered also. One should consider the potential side effects and interaction with other medications when choosing an agent [39].

Uremic Neuropathy

Neuropathy is a common complication of end-stage kidney disease, typically presenting as a distal symmetric process similar to diabetic neuropathy. Many of these patients also have diabetes making it difficult to determine the etiology of the neuropathy. Autonomic features may be present. Nerves of uremic patients have been shown to exist in a chronically depolarized state with the degree of depolarization corresponding to serum potassium levels [40]. It is thought that maintenance of near normal potassium levels may improve symptoms. Renal transplantation has been shown to rapidly reverse the symptoms of uremic neuropathy.

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Toxin Induced

Toxic neuropathies develop over several weeks to months as a result of continued exposure to various drugs, industrial toxins, or heavy metals. A progressive, symmetric, ascending polyneuropathy is most frequently seen with occupational exposures. The most commonly implicated drugs include antineoplastic agents, particularly cisplatin and vinca alkaloids, antiretroviral drugs (didanosine, zalcitabine, stavudine), as well as isoniazid, dapsone, and amiodarone. Rare cases of arsenic poisoning, either intentional or from insecticide exposure, may cause a delayed-onset progressive polyneuropathy. Chronic lead exposure causes a predominantly motor neuropathy, typically beginning in the upper limbs, with asymmetric radial neuropathy and wrist-drop. A careful review of potential occupational exposures is the key to diagnosis of neuropathy caused by heavy metals and industrial toxins.

Chemotherapy-induced peripheral neuropathy is predominantly a sensory neuropathy but may have motor and autonomic changes. There is no effective prevention strategy for this condition, and onset generally requires a dose reduction or cessation of the chemotherapeutic agent. The prevalence is 68.1% in the first month after chemotherapy and falls to 30% 6 months after chemotherapy [41]. Risk factors for development of chemotherapy-induced peripheral neuropathy are baseline neuropathy, smoking, abnormal creatinine clearance, and specific sensory changes during chemotherapy [41]. Medications used to treat other neuropathic pain conditions have not been shown to be successful with the exception of one study showing improvement after 5 weeks of treatment with duloxetine [42].

Nutritional Neuropathies

Malnutrition may affect all areas of the nervous system. Risk factors for malnutrition include alcoholism, eating disorders, older age, homelessness, and lower socioeconomic status. Absorption of nutrients may be impaired by several conditions including inflammatory bowel disease, fat malabsorption, chronic liver disease, bowel resection, gastric bypass, and celiac disease.

Alcoholic Neuropathy

The polyneuropathy related to chronic alcoholism is clinically indistinguishable from that due to vitamin deficiencies and may be better classified as toxin induced. The most important risk factor is total lifetime dose of alcohol. Prevalence is 46% when confirmed by nerve conduction studies. Alcohol causes deficiencies by replacing more nutritious foods in the diet, by increasing the requirements for B vitamins (which are needed for its metabolism), and perhaps by impairing vitamin absorption. Alcohol may also have a direct toxic effect on peripheral nerves: in a few patients, a neuropathy occurs despite an adequate diet. The prognosis for ultimate, but slow, recovery is good for patients who are able to stop drinking and resume a proper diet with multivitamin supplements [43].

Vitamin B1 (Thiamine) Deficiency

Neuropathy due to thiamine deficiency or beriberi is associated with alcoholism, recurrent vomiting, AIDS, long-term total parenteral nutrition, eating disorders, and bariatric surgery. It is also responsible for Wernicke's encephalopathy and Korsakoff's syndrome. Features include sensory loss, burning pain, or muscle weakness in the toes and feet. If untreated, the neuropathy will ascend. It may also involve the recurrent laryngeal nerve or cranial nerves manifesting with hoarseness and tongue and facial weakness. Thiamine replacement can occur either intravenously or intramuscularly at an initial dose of 100 mg daily. Symptoms may take 3–6 months to resolve [44].

Vitamin B6 (Pyridoxine) Deficiency and Toxicity

Vitamin B6 can cause neuropathy both in deficiency and excess. Dietary deficiency is rare; however, many medications interfere with B6

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metabolism. Culprits include isoniazid, phenelzine, hydralazine, and penicillamine. It may also be seen in alcoholics, patients on dialysis, and pregnant or lactating women due to high metabolic needs. Symptoms of deficiency are numbness, paresthesias, and burning pain in the feet that ascends. Examination will show decreased distal sensation, reduction of deep tendon reflexes, ataxia, and mild distal weakness. Toxicity causes sensory ataxia, areflexia, and impaired cutaneous sensation. Prophylactic doses of pyridoxine 50 mg per day are recommended for those treated with isoniazid or hydralazine and 10–50 mg for those undergoing dialysis [44].

Vitamin B12 Deficiency

Vitamin B12 is found in animal and dairy products and is liberated from food by stomach acid. Persons at risk for B12 deficiency include patients with malabsorption, pernicious anemia, gastrointestinal surgeries, and strict vegan diets. Additionally, prolonged use of metformin, proton pump inhibitors, and H2 blockers has been implicated. The neuropathy usually presents with sensory symptoms in the feet and may be associated with anemia or normal blood counts. Patients have increased tone, loss of proprioception and vibration, weakness in the corticospinal tract (hip and knee flexors), brisk reflexes, and extensor plantar responses in the toes. Diagnosis is made with serum levels less than 200 pg/mL or in the low normal range up to 400 pg/mL. Measuring serum methylmalonic acid or homocysteine may improve sensitivity. Treatment is with administration of B12 1000 mcg intramuscularly for 5–7 days followed by 1000 mcg monthly or alternatively starting with once weekly injections for 4 weeks followed by monthly. Oral therapy is as effective in doses of 1–2 mg daily, though improvement is slower than with injection therapy [44].

Vitamin E Deficiency

Vitamin E is a fat-soluble vitamin; therefore deficiency may take 5–10 years to manifest. Symptoms mimic Friedreich's ataxia with ataxia, hyporeflexia, and loss of proprioception and vibration. Diagnosis is made with alpha-tocopherol levels in the serum. Treatment is with oral supplementation of 400 international units twice daily until normalization of levels. Those with malabsorption syndromes may require water-soluble or intramuscular preparations [44].

Copper Deficiency

Copper deficiency can cause both a peripheral neuropathy and myelopathy. It is mainly caused by prior gastric surgery or excessive zinc intake. Patients present with gait difficulty and lower limb paresthesias. Exam will reveal loss of proprioception and vibration in addition to sensory ataxia. There may also be upper motor neuron signs such as bladder dysfunction, brisk knee jerks, and extensor plantar reflexes. MRI may show increased signal in the posterior columns. Serum levels of copper, ceruloplasmin, and urinary excretion of copper will be low in addition to anemia. If deficiency is due to excessive exogenous zinc, this should be discontinued. Replacement with 2 mg of elemental copper three times daily via oral route is preferred [44].

Hereditary Neuropathies

Hereditary neuropathies are estimated to occur in 1 per 10,000 individuals. Due to the slowly progressive, indolent course of these disorders, many patients do not recall other family members being affected, and in some cases they do not recognize the abnormalities in themselves. The hereditary neuropathies are typically associated with foot drop, high-arched feet (pes cavus), hammertoe deformities, slowly progressive weakness and wasting of peroneal muscle groups, and a high-stepping, slapping gait. Sensory symptoms are much less prominent.

The genetics and pathophysiology of numerous hereditary neuropathies have been elucidated; however, just two types of hereditary motor and sensory neuropathies (HMSN I,

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HMSN II) represent virtually all forms of this disorder. HMSN I, a demyelinating process with onset during the teenage years, constitutes roughly 70% of the hereditary neuropathies. Nearly all other hereditary neuropathies are HMSNII (formerly called Charcot-Marie-Tooth or peroneal muscle atrophy), a primarily axonal degeneration with secondary demyelination that occurs during the fourth decade of life or later. These two types share an autosomal dominant inheritance; however, many subtypes have been identified with varying inheritance patterns. Specific genetic tests are now available to confirm the diagnosis of many of the hereditary neuropathies [45].

There is no specific treatment for any of these disorders; genetic counseling and education are needed. Patients with this disorder frequently have deformities of the foot that can be managed with physical therapy. Disability varies widely between families. Animal trials have shown promise using ascorbic acid and progesterone antagonists. Clinical studies are ongoing.

Treatment

Appropriate treatment for any underlying diseases should be instituted (e.g., control of glucose, thyroid replacement). Offending toxins or medications should be stopped and nutritional deficiencies corrected. Other disease-specific treatments are addressed above.

Neuroleptic drugs and tricyclic antidepressants have been the mainstay of treatment for neuropathic pain. Patients can be started on amitriptyline, duloxetine, gabapentin, or pregabalin initially [29]. Gabapentin and pregabalin have the best evidence for treatment of painful diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain [46]. Gabapentin and carbamazepine also show efficacy in treatment of pain associated with Guillain-Barre syndrome [35]. Other neuroleptics may have benefit in individual patients. Tramadol may be considered for acute pain, but opioids are not recommended for chronic treatment of neuropathic pain as they have questionable efficacy with deleterious side effects and safety concerns [42]. Capsaicin and lidocaine patches have weak evidence in support of their use in peripheral neuropathic pain only [1]. Interventional treatments such as nerve blocks or surgical procedures may be considered for patients with refractory neuropathic pain. Botulinum toxin A has shown some promise in treating areas of muscle hyperactivity associated with neuropathy. [47].

Psychological interventions may be considered for comorbid mood disorders and sleep disturbances. Their evidence for improving neuropathic pain is weak at best [48].

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Selected Disorders of the Nervous System

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Meningitis

Background

Meningitis is defined as an acute inflammation of the meninges, which may result in significant morbidity and mortality. Meningitis may be caused by infectious agents (bacteria, viruses, parasites, and fungi) or may arise from a noninfectious etiology (cancer, systemic lupus erythematosus, certain medications, head injury, and brain surgery). When caused by an infectious agent, approximately one in four cases of meningitis is bacterial, with an additional 10% due to fungus and other nonviral agents. The remainder is due to viruses. In the United States, bacterial meningitis occurs at a rate of 1.38 cases per 100,000 population per year, with a case fatality of approximately 15%. The causative bacterial agent varies with age. Under 2 months of age, group B streptococcus is the most common bacterial agent, and in those 11–17 years of age, *Neisseria meningitides* is the most common bacterial agent. In all other pediatric age groups and in adults, *Streptococcus pneumonia* is the most common bacterial agent. Viral meningitis is most commonly caused by enteroviruses followed by herpes simplex virus type 2 and varicella zoster virus. Fungal infections are a rare cause and most common in immunocompromised individuals [1].

Presentation

About half (44%) of adults will have a "textbook" presentation of meningitis, the triad of fever, neck stiffness, and change in mental status. However, the most frequent symptom in adults subsequently found to have meningitis is headache, followed by neck stiffness, fever, and change in mental status. Using a dyad (two of four of the following: headache, fever, neck stiffness, or a change in mental status) increased the positive predictive value to 95%. Only 4% of patients subsequently diagnosed with meningitis had one symptom, with 1% having none of the four symptoms. The clinical presentation of meningitis for children under the age of 3 is usually more subtle and atypical, may not have any of the four cardinal symptoms, and may present only with irritability and lethargy.

Diagnosis

History

Aside from making the diagnosis, a carefully taken history is important to determine if there are any predisposing or complicating factors. These include infectious illness, immunocompromised state, previous neurosurgical procedure, and immunization status. However, clinical history alone is not sufficient to diagnose meningitis.

Physical Examination

The physical exam for meningitis is focused on finding and documenting neurologic deficits on presentation. In addition to documenting meningeal signs (jolt accentuation of headache, Kernig's and Brudzinski's signs), the physical exam should include an assessment of the rest of the neurologic system including the Glasgow Coma Score. The presence of meningeal irritation is assessed by laying the patient supine and gently flexing the neck

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forward while examining the neck for rigidity. Kernig's sign is performed with the patient supine and the hip flexed to 90°. A positive sign is present when extension of the knee from this position elicits resistance or pain in the lower back or posterior thigh. Brudzinski's sign is present with passive neck flexion in a supine position results in flexion of knees and hips. The jolt accentuation of headache is positive if the patient's headache worsens when turning his or her head horizontally 2–3 rotations per second. The classic triad of fever, neck stiffness, and a change in mental status is present in only about 44% of episodes, but 95% of cases had at least two of four symptoms of headache, fever, neck stiffness, and altered mental status. Since these bedside diagnostic tools have poor sensitivity, further diagnostic testing should not be precluded by the absence of these clinical signs [2].

Cerebrospinal Fluid Examination

Prompt examination of the cerebrospinal fluid (CSF) is required for diagnostic confirmation of meningitis. Imaging for intracranial lesions should be performed prior to lumbar puncture (LP) in patients with altered mentation, focal neurological findings, and papilledema or if there is clinical suspicion of increased cranial pressure. Other relative contraindications to performing a lumbar puncture include local infection at the puncture site, recent administration of anticoagulation within the past hour, and platelet count less than $20 \times 10^3/\mu L$. Videos of how to perform a LP are readily available online.

When possible, opening pressure of the CSF within the spinal canal should be documented. Normal opening CSF pressure is 10–100 mm H_2O in young children, 60–200 mm of H_2O after 8 years of age, and up to 250 mm of H_2O in obese patients. 1–5 ml samples of CSF are normally placed into four tubes, numbered in the order in which they were collected. Tube 1 is used for cell count, tube 2 for protein and glucose, tube 3 for specific tests as indicated (e.g., latex agglutination for bacterial and viral antigens, polymerase chain reaction), and tube 4 for cultures. Normal values are easily obtained from multiple references and may vary with the patient's underlying condition [3].

Laboratory Testing and Imaging

Additional testing should include a complete blood count with differential, complete metabolic panel, and blood culture. Cultures should be obtained from blood as well as other potential sources of infection. Additional imaging performed should be obtained as warranted by clinical suspicion.

Treatment

Antibiotic therapy should be initiated as soon as possible after the diagnosis of meningitis is entertained and should not be delayed to obtain a CSF sample. Antibiotic choice is dependent on age, comorbidities (e.g., immunodeficiency, prior neurosurgical procedures), and situation (e.g., head trauma). For most suspected meningitis cases, an initial broad-spectrum approach such as vancomycin and a third-generation cephalosporin is suggested as an empiric antibiotic regimen with subsequent changes based on culture results. For adults older than 50 years, the regimen should include ampicillin, as well as vancomycin and a third-generation cephalosporin. For infants younger than 1 month, the suggested empiric antibiotic regimen should include ampicillin and cefotaxime or ampicillin and an aminoglycoside. The use of dexamethasone remains controversial. If herpes simplex meningitis is clinically suspected, empiric treatment should include acyclovir. For uncomplicated cases of viral meningitis, no specific antibiotic therapy is necessary [4].

Course and Prognosis

Without treatment, mortality of patients with bacterial meningitis approaches 100%. However, even with treatment, the mortality rate in the United States is still 15%. This has improved significantly since the routine vaccination for Hib in the early 1990s. Hearing loss is seen in 14% of adult patients and hemiparesis in 7% of adult patients. Stroke is seen in 3% of children [5, 6].

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Special Considerations

Chronic Meningitis

Chronic meningitis is defined as "irritation and inflammation of the meninges persisting for more than 4 weeks associated with pleocytosis in the cerebrospinal fluid." Chronic meningitis may be caused by persistent infection, allergic inflammatory reaction to an infection, autoimmune disease, or chemical and drug exposure. Clinical presentation is often nonspecific and only becomes similar to that of acute meningitis over time. The approach to diagnosis is necessarily broad, but an accurate and detailed history and physical exam will help to narrow the differential diagnosis. Up to one-third of patients with chronic meningitis will not have a definitive diagnosis even after a thorough and complete investigation [7].

Noninfectious Meningitis

Medications [trimethoprim–sulfamethoxazole (Bactrim), ibuprofen (Motrin), and naproxen (Naprosyn)] and medical procedures (intrathecal injections and neurosurgical procedures) can rarely cause noninfectious meningitis. Brain tumors may cause "chemical" meningitis due to the lipid-induced chemical irritation and may require repeated LPs and careful examination of CSF for diagnosis. Connective tissue diseases and vasculitis syndromes have been reported to be associated with noninfectious meningitis, especially sarcoidosis, systemic lupus erythematosus, and Behçet's disease [8].

Prevention

Vaccines as primary prevention have been successful in greatly reducing the incidence of bacterial meningitis in children and adults – especially since their addition to the childhood vaccine schedule. Vaccines are available for *Haemophilus influenzae* type b, *Neisseria meningitis*, and *Streptococcus pneumonia*. Guideline for chemoprophylaxis for close contacts of individuals diagnosed with bacterial meningitis is available. In addition, universal screening of all pregnant women for group B streptococcal disease with subsequent treatment during labor has caused a marked decline in perinatal group B streptococcal disease [6].

Encephalitis

Background

Encephalitis is the presence of an inflammatory process of the parenchyma of the brain in association with clinical evidence of neurological dysfunction. Encephalitis can be caused by a large variety of pathogens. Of the cases where an etiology was identified, most were viral, followed by bacterial, prion-related, parasitic, and fungal etiologies. In the majority of cases, an etiology will not be identified. In the United States, the most commonly identified etiologies are herpes simplex virus (HSV), West Nile virus, and enteroviruses, followed by other herpesviruses. Exposure can be immediately proximate to the onset of symptoms or delayed such as encephalitis associated with measles, congenital rubella, or HIV. HSV encephalitis can be either acute (33%) or the result of reactivation of latent infection (66%).

Presentation

The presentation of encephalitis is very similar to that of meningitis and includes fever, headache, nausea and vomiting, and altered level of consciousness often associated with seizures and focal neurological findings. Other common findings include disorientation, speech disturbances, and behavioral changes. Alterations in mental functions may cause lethargy, drowsiness, confusion, disorientation, and coma.

Diagnosis

History and Physical Exam

As the differential diagnosis of encephalitis is broad, a thorough history and physical exam are necessary to narrow the differential diagnosis list. Helpful questions to ask during history taking to determine the etiology include age, animal contact, immunocompromised states, ingested items, insect contact, occupation, recent sick contacts, recent vaccinations, recreational activities, season, transfusion and

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Table 1 Findings associated with specific etiologies

Etiology	Findings
Herpes simplex virus	Frontotemporal signs Mucous membrane lesions
Rabies	Psychomotor excitation Bulbar dysfunction and spasm
Creutzfeldt–Jakob disease	Subacute personality changes Dementia with myoclonus

Adapted from Refs. [9, 10]

transplantation, travel history, and vaccination status. A detailed physical exam with careful attention paid to a careful neurological exam may be helpful in narrowing the differential diagnosis list as certain physical exam findings are associated with specific etiologies (see Table 1).

Laboratory Testing

Cerebrospinal fluid (CSF) analysis is essential to diagnosis in all patients with encephalitis (unless contraindicated) and will typically demonstrate lymphocytic pleocytosis with normal glucose and a modest elevation of protein. CSF should be analyzed for virus-specific IgM antibodies and nucleic acid amplification – especially herpes simplex polymerase chain reaction (PCR). Other studies should include complete blood count; tests of renal and hepatic function; coagulation studies and chest radiography; cultures of body fluid specimens; biopsy of specific tissue for cultures, antigen detection, nucleic acid amplification tests, and histopathology examination; serological testing of IgM antibodies; acute- and convalescent-phase serum samples for retrospective diagnosis of an infectious agent; nucleic acid amplification of body fluids outside of the CNS; and peripheral blood smear. Additional diagnostic studies should be performed on the basis of specific epidemiological and clinical clues.

Imaging

Magnetic resonance imaging (MRI) of the brain is the most sensitive neuroimaging test to evaluate patients with encephalitis, although computerized tomography (CT), with and without contrast, should be used in patients if MRI is unavailable, impractical, or cannot be performed. MRI may show characteristic patterns seen with specific agents in patients with encephalitis.

Treatment

All patients with encephalitis should empirically be started on acyclovir (Zovirax) 10 mg/kg (500 mg/m^2 for children <12 years) IV infused over 1 h every 8 h for 14–21 days pending results of diagnostic tests and elimination of the possibility of HSV as a causative agent. Other antimicrobial agents should be started on the basis of specific epidemiological or clinical factors, including appropriate therapy for bacterial meningitis. In patients with clinical and epidemiological clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline (Vibramycin) 100 mg twice daily for 10–14 days should be added to the empirical regimen. Specific therapy should be tailored based on the results of diagnostic testing.

Course and Prognosis

Morbidity and mortality remain high with encephalitis. Poor prognostic factors include age above 60, reduced Glasgow Coma Score on admission, and, for HSV encephalitis, delay between hospitalization and starting treatment with acyclovir. The mortality rate for encephalitis is dependent on the causative organism ranging from less than 5% with ehrlichiosis to 33% with Eastern equine encephalitis virus to 100% with rabies. In addition, approximately two-thirds of survivors will have significant neuropsychiatric sequelae

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including memory impairment, personality and behavioral change, dysphagia, and seizures [9–11].

Brain Abscess

Background

Brain abscesses, or focal intracerebral infections consisting of an encapsulated collection of pus caused by bacteria, mycobacteria, fungi, protozoa, or helminths, are most commonly caused by bacteria. *Streptococcus* species is the most common causative agent, followed by *Staphylococcus* species, then gram-negative enteric species. Brain abscesses are rare, with the incidence estimated to be 0.3–1.3 per 100,000 people per year. The incidence is significantly higher in developing countries and in patients who are alcoholic, are immunosuppressed (e.g., acquired immune deficiency syndrome, chemotherapy, biologic drugs), have cyanotic heart conditions, or are severely debilitated by neurological conditions. Brain abscesses most often arise from direct invasion from a contiguous focus of infection (i.e., otitis, mastoiditis, sinusitis, meningitis, and odontogenic). They can also be secondary to blood-borne pathogens (i.e., pulmonary focus or heart disease) or arise in areas of previous head trauma.

Presentation

An area of damaged brain tissue allows a nidus of infection to occur with subsequent local areas of infarction. Cerebritis follows as the area becomes necrotic and encapsulated within a few weeks. Presentation is dependent on mechanism and pathogen, which includes focal mass expansion, increased intracranial pressure, diffuse destruction, or focal neurological deficit. Clinical signs and symptoms of brain abscesses are varied and commonly include fever, headache, hemiparesis of a cranial nerve, hemiparesis, meningism, altered level of consciousness, seizure, nausea and vomiting, and papilledema.

Diagnosis

Physical Exam

The most common symptoms of brain abscess are headache (69%), fever (53%), and focal neurological deficits (48%). However, as a triad, the three together only occur in 20% of patients with brain abscesses. A high index of suspicion is required to make the diagnosis, particularly in febrile patients with a history of central nervous system instrumentation.

Laboratory Studies

Laboratory studies, such as blood cultures, complete blood count, and chest radiograph, are commonly performed, but may not provide useful data, as only 28% of blood cultures were positive in one study. CSF cultures are often sterile, and lumbar puncture is not recommended and may be contraindicated due to increased intracranial pressure.

Neuroimaging

Diagnosis is dependent on neuroimaging. Classically, a hypodense lesion with a contrast-enhancing ring will be seen on computed tomography (CT) of the brain or magnetic resonance imaging (MRI) of the brain. CT of the brain allows for detection, localization, characterization, and is ubiquitous in emergency departments. In addition, CT of the brain can detect hydrocephalus, increased intracranial pressure, edema, and other associated infections. However, CT of the brain has a 6% false-negative rate. Diagnosis of brain abscess by MRI of the brain is more accurate than CT, but MRI is not as ubiquitous or available as CT and so is less commonly used.

Treatment

Treatment of brain abscess requires a combination of antibiotic treatment, surgical intervention, and eradication of the primary foci. Successful treatment of brain abscesses often requires drainage under CT guidance in addition to antibiotic therapy.

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Antibiotic Therapy

Until the abscess can be drained and cultured, empiric antibiotic therapy should consist of broad-spectrum antibiotics that easily cross the blood–brain, and blood–CSF barriers should provide coverage for the most common pathogens. Acceptable antibiotic choices include a third-generation cephalosporin and metronidazole. Vancomycin should be added if there is a history of penetrating trauma or recent neurosurgical procedure. Antibiotic therapy should be tailored for patients with specific immune function defects, transplant recipients, cancer, and on chronic steroid therapy. However, as cultures are often sterile, broad-spectrum antibiotics should be continued for the entire course.

Duration of antimicrobial therapy has been suggested to be 4–6 weeks for a surgically drained abscess, 6–8 weeks for a brain abscess solely treated with antibiotics, and 3–12 months for immunocompromised patients.

Neurosurgical Intervention

Emergent drainage of brain abscesses is indicated as part of the management and to establish the causative pathogen due to the high sterile culture rate. Aspiration has become the preferred method for drainage providing relief from increased intracranial pressure and avoids the possibility of damage to the surrounding brain. However, aspiration often (70%) requires repeat procedure and can possibly cause iatrogenic puncture of the ventricle and subarachnoid leakage of pus leading to extension of the brain abscess.

Adjunctive Therapy

Steroids are generally avoided except in the perioperative period. They are indicated for reduction of intracranial pressure and avoiding acute brain herniation in those patients that demonstrate signs of meningitis or disproportionate cytotoxic edema posing a life-threatening problem. Steroids should be tapered as rapidly as possible.

Anticonvulsants are commonly used to control seizures and are used as prophylaxis for subsequent seizures after resolution of brain abscesses. Anticonvulsants are recommended to be continued for 5 years after resolution of the brain abscess. However, discontinuing anticonvulsants may be considered if the patient has been seizure-free for 2 years after surgery and no epileptic activity is seen on electroencephalography (EEG). The law regarding driving with a diagnosis of seizure is dependent on the state, but usually requires being seizure-free for 6–12 months prior to resumption of driving.

Course and Prognosis

The mortality rate of brain abscesses has declined by 50%, from 20% to 10% in recent years. Approximately half of patients will have a good outcome, but the other half will either die or have neurological sequelae. Poor prognostic indicators include delayed diagnosis, rapidly progressing disease, coma, multiple lesions, intraventricular rupture, and fungal etiology. Outcomes are worse in the elderly and newborn. Neurological sequelae include focal neurologic deficits, intellectual disability, and postoperative seizures [12–14].

Neurosyphilis

Background

Syphilis is a sexually acquired condition caused by infection with *Treponema pallidum* and is known as the "great imitator" due to its varied presentation. Although syphilis was close to eradication in 2000, in the years between 2005 and 2013, syphilis has increased in annual rate from 2.9 to 5.3 cases per 100,000 population [15].

Presentation

Syphilis is divided into primary infection (ulcer or chancre), secondary infection (skin rash, mucocutaneous lesions, lymphadenopathy), neurologic infection (cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities), and tertiary infection (cardiac or

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gummatous lesions). However, neurosyphilis can occur at any stage of infection and has three distinct patterns of occurrence. Asymptomatic neurosyphilis is defined as the presence of cerebrospinal fluid (CSF) abnormalities consistent with neurosyphilis in persons with serological evidence of syphilis and no neurological signs or symptoms. Early symptomatic neurosyphilis involves diffuse inflammation of the meninges and presents similarly to meningitis – headache, photophobia, nausea, vomiting, cranial nerve palsies, and occasionally seizures. Lastly, meningovascular syphilis consists of endarteritis of vessels anywhere in the central nervous system resulting in thrombosis and infarction.

Headache, vertigo, and insomnia often occur early in the course of infection. Dramatic symptoms such as the sudden onset of contralateral hemiparesis, hemianesthesia, homonymous hemianopsia, and aphasia lead to a more rapid diagnosis. Symptoms of syphilis involving the spinal cord include spastic weakness of the legs, sphincter disturbances, sensory loss, and muscle atrophy. Parenchymatous syphilis may manifest as either paretic neurosyphilis ("general paralysis of the insane") or tabetic neurosyphilis ("tabes dorsalis"). Early symptoms of paretic neurosyphilis include irritability, forgetfulness, personality changes, headaches, and changes to sleep habits, while late symptoms include emotional liability, impaired memory and judgment, disorientation, confusion, delusions, seizures, and other psychiatric symptoms. Tabetic neurosyphilis presents classically as ataxic gait, lightening pains, paresthesias, bladder dysfunction, and failing vision.

Diagnosis

Physical Exam

Depending on the stage and presentation of neurosyphilis, the physical exam may be unremarkable or may be similar to other disease processes. Physical exam findings may include papillary abnormalities (Argyll Robertson pupils), diminished reflexes, impaired vibratory sense and proprioception, ocular palsies, and Charcot joints (progressive degeneration of weight-bearing joints) [16, 17].

Laboratory Studies

The diagnosis of syphilis is made using a combination of serological tests [Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR)], treponemal tests [fluorescent treponemal antibody absorbed (FTA-ABS) or *T. pallidum* passive particle agglutination (TP-PA)], or dark-field examination. Laboratory testing can only be used to support the diagnosis of neurosyphilis, but no single test can be used to diagnose neurosyphilis in all circumstances. The identification of serologic changes in the cerebrospinal fluid (CSF-VDRL) has a high specificity, but low sensitivity. CSF-VDRL can be positive in early syphilis, but is a finding of uncertain significance. CSF can be tested for treponemal antibodies using FTA-ABS. This is more sensitive than CSF-VDRL, but less specific. Therefore, diagnosis of neurosyphilis is a combination of reactive serological test results and a reactive CSF-VDRL, in the presence of signs of CSF inflammation (elevated cell count and protein), with or without clinical manifestations.

Treatment

Antimicrobial Treatment

Penicillin is the preferred drug for treating all stages of syphilis – including in pregnancy. Those with a penicillin allergy should undergo desensitization and be treated with penicillin.

A frequent reaction to the administration of penicillin G at any stage of syphilis is the Jarisch–Herxheimer reaction, which is an acute febrile reaction frequently accompanied by headache, myalgia, and fever. Although this may induce early labor or fetal distress in pregnant women, this should not delay or prevent therapy.

Penicillin G 18–24 million units per day is the preferred dosage and should be administered as 3–4 million units by IV every 4 h or as a continuous infusion for 10–14 days. If

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compliance is an issue, an alternative regimen is procaine penicillin 2.4 million units once daily and probenecid 500 mg orally four times daily for 10–14 days.

If CSF pleocytosis was present initially on examination, repeat CSF examination should occur every 6 months until the cell count is normal. If cell count or protein is not normal after 2 years, retreatment should be considered.

Special Considerations

Persons who are exposed to syphilis via intimate contact at any stage should be evaluated clinically and serologically. If the exposure was within 90 days preceding the diagnosis of any stage of syphilis – even if the exposed person is seronegative – he or she should be treated presumptively. Persons who are exposed 90 days or more prior to diagnosis of any stage of syphilis in a sex partner should have serologic testing prior to treatment. However, the exposed person should be treated presumptively if serological testing is not available immediately and follow-up is uncertain. In addition, intimate partners of infected patients should be provided presumptive treatment if they have had sexual contact with the patient within 3 months plus the duration of symptoms for primary syphilis, within 6 months plus duration of symptoms for secondary syphilis, and within 1 year for patients with early latent syphilis [18].

Brain Tumors

Background

Primary brain tumors are rare, accounting for 1.4% of all new cancer cases with an incidence of 5.42 per 100,000 children aged 0–19 years and 27.9 per 100,000 adults aged 20 years and older. Approximately 34% of all primary brain tumors are malignant. The most common types of primary brain tumor are malignant glioblastoma and meningioma. In adults, the most common types of primary brain tumor are glioblastoma, meningioma, astrocytoma, and pituitary adenoma, while in children, the most common types of primary brain tumors are tumors of pilocytic astrocytoma, embryonal tumors, and malignant glioma (see Table 2) [19].

Metastatic disease to the CNS is much more common than primary brain tumors occurring up to ten times as often as primary brain tumors. Although primary lung cancers are the most common source of metastatic lesions, melanoma and breast cancer are becoming more frequent. Approximately 80% of brain metastases occur in the cerebral hemispheres, followed by 15% in the cerebellum, and 5% in the brainstem.

Presentation

The presenting signs and symptoms of metastatic brain lesions are similar to other mass

Table 2 Distribution of primary brain tumors by histology

Histology	Percentage of total
Meningioma	36.1%
Glioblastoma	15.4%
Tumors of the pituitary	15.1%
Nerve sheath tumors	8.0%
All other astrocytomas	6.0%
Lymphomas	2.1%
Ependymal tumors	1.9%
Oligodendrogliomas	1.6%
Embryonal tumors	1.1%
Oligoastrocytic tumors	0.9%
All other	11.8%

Adapted from Ref. [18]

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Table 3 Red flag symptoms that should prompt immediate imaging

Red flag	Differential diagnosis
Headache beginning after 50 years of age	Temporal arteritis, mass lesion
Sudden onset of headache	Subarachnoid hemorrhage, pituitary apoplexy, hemorrhage into a mass lesion or vascular malformation, mass lesion
Headaches increasing in frequency and severity	Mass lesion, subdural hematoma, medication overuse
New-onset headache in a patient with risk factors for HIV infection or cancer	Meningitis (chronic or carcinomatous), brain abscess (including toxoplasmosis), metastasis
Headache with signs of systemic illness (fever, stiff neck, rash)	Meningitis, encephalitis, Lyme disease, systemic infection, collagen vascular disease
Focal neurological signs or symptoms of disease (other than typical aura)	Mass lesion, vascular malformation, stroke, collagen vascular disease
Papilledema	Mass lesion, pseudotumor cerebri, meningitis
Headache subsequent to head trauma	Intracranial hemorrhage, subdural hematoma, epidural hematoma, posttraumatic headache

Adapted from Ref. [20]

lesions and can be separated into focal or generalized symptoms. Focal symptoms are dependent on tumor location. For example, focal symptoms of brain tumors in the frontal lobe include dementia, personality changes, gait disturbance, expressive aphasia, and seizures; in the parietal lobe include receptive aphasia, sensory loss, hemianopia, and spatial disorientation; in the temporal lobe include complex partial or generalized seizure, behavior change, including symptoms of autism, and quadrantanopia; in the occipital lobe include contralateral hemianopia; in the thalamus include contralateral sensory loss, behavior change, and language disorder; in the cerebellum include ataxia, dysmetria, and nystagmus; and in the brainstem include cranial nerve dysfunction, ataxia, papillary abnormalities, nystagmus, hemiparesis, and autonomic dysfunction. Generalized symptoms include headache, memory loss, cognitive changes, motor deficit, language deficit, seizures, personality change, visual problems, changes in consciousness, nausea or vomiting, sensory deficit, and papilledema [20].

Diagnosis

Diagnosis is dependent on appropriate brain imaging followed by histopathology to confirm diagnosis. Acute headaches with red flag symptoms should prompt immediate imaging (see Table 3) [21].

The imaging modality of choice is gadolinium-enhanced magnetic resonance imaging (MRI). For those who cannot have a MRI performed, computed tomography (CT) of the head and spine is acceptable; however, CT does not have as high of a resolution as MRI and is unable to adequately assess lesions in the posterior fossa and spine.

Treatment

Due to the varied course and symptoms of primary and metastatic brain tumors, prognosis and treatment are highly individualized and are dependent on age and performance status of the patient, proximity to "eloquent" areas of the brain, feasibility of decreasing the mass effect, resectability of the tumor, and time since last surgery for those with recurrent disease. In general, regardless of tumor histology, the best outcome is through a combination of maximal safe resection (stereotactic biopsy, open biopsy, subtotal resection, or complete resection) and radiation therapy (brachytherapy, fractionated external beam radiotherapy, or fractionated stereotactic radiotherapy). Whole brain radiotherapy and stereotactic radiosurgery is often reserved for metastatic disease.

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Symptom Treatment

Corticosteroids may be necessary to treat vasogenic edema. Often, corticosteroids need to be tapered slowly, although side effects of long-term use of corticosteroids include cognitive impairment, hypoglycemia, gastrointestinal problems, myopathy, and opportunistic infections. Seizures are common with brain tumors, including after surgery. However, prophylactic use of antiseizure medications is not indicated [22].

Course and Prognosis

Prognosis is dependent on histopathology (oligodendrogliomas have a better prognosis than mixed gliomas, which have a better prognosis than astrocytomas) and tumor grade. Younger age, good initial performance score, and O6-methylguanine methyltransferase (MGMT) gene promoter hypermethylation are associated with a more favorable prognosis [23].

Multiple Sclerosis

Background

Multiple sclerosis (MS) is a disabling demyelinating immune-mediated disease of the central nervous system (CNS) that disproportionately affects women, smokers, persons living at higher latitudes, and persons with a family history of MS. Increased exposure to sunlight and higher 25-hydroxyvitamin D levels confer lower risk. The incidence of MS ranges from 47.2 to 109.5 per 100,000 persons in the United States [24].

Presentation

The clinical presentation of MS is varied and can include symptoms such as depressed mood, dizziness or vertigo, fatigue, hearing loss and tinnitus, loss of coordination and gait disturbance, pain, sensory disturbances (dysesthesias, numbness, paresthesias), urinary symptoms, visual disturbances (diplopia and oscillopsia), and weakness and can include signs such as ataxia, decreased sensation (pain, vibration, position), decreased strength, hyperreflexia, spasticity, nystagmus, and visual defects (internuclear ophthalmoplegia, optic disk pallor, red color desaturation, or reduced visual acuity) [25, 26].

Diagnosis

History, Physical Exam, and Diagnostic Imaging

The current guideline for diagnosis of multiple sclerosis (MS), the 2010 revisions to the McDonald Criteria, requires a combination of history, physical exam, and diagnostic imaging. An attack is defined as "patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS), current or historical, with duration of at least 24 h, in the absence of fever or infection." The diagnostic criteria for MS based on clinical presentation are listed in Table 4 [27]. MS-typical regions of the CNS include periventricular, juxtacortical, infratentorial, or spinal cord.

Differential Diagnosis

MS has a broad differential diagnosis, and consideration should be given to testing angiotensin-converting enzyme levels, autoantibody titers, *Borrelia* titers, human immunodeficiency virus (HIV) screening, rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), thyroid-stimulating hormone, and vitamin B12 level.

Treatment

Disease-Modifying Agents

The mainstay of treatment of MS is disease-modifying agents, which slow disease progression, preserve function, and sustain the immune system while suppressing the T-cell autoimmune cascade. Approved disease-modifying agents, which include interferon beta, glatiramer, fingolimod, teriflunomide, dimethyl fumarate, natalizumab, and mitoxantrone, are usually managed by an experienced neurologist.

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Table 4 Diagnostic criteria for multiple sclerosis

Clinical presentation	Additional data needed for MS diagnosis
≥2 attacks; objective clinical evidence of ≥2 lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack	None
≥2 attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS Awaiting another clinical attack implicating a different CNS site
One attack; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time A new T2 and/or gadolinium-enhancing lesion (s) on follow-up MRI, irrespective of its timing with reference to a baseline scan Await a second clinical attack
One attack; objective clinical evidence of one lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS Await a further clinical attack implicating a different CNS site For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan Await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively determined) plus two of three of the following criteria: 1. Evidence for DIS in the brain based on ≥1 T2 lesion in at least two of four MS-typical regions of the CNS 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Adapted from Ref. [26]

Exacerbations

Exacerbations are common, affecting over 85% of patients with MS, and are often caused by infection or stress. Oral corticosteroids are the mainstay of the treatment of exacerbations. However, if there is no response to corticosteroids, plasmapheresis or plasma exchange may be performed.

Symptom-Specific Management

Neurogenic bladder, affecting more than 70% of patients with MS, may be alleviated with anticholinergic medications for failure-to-store symptoms; limiting evening fluid intake, desmopressin, or injections of onabotulinumtoxinA for nocturia; and clean intermittent catheterization or alpha-adrenergic blockade for failure-to-empty symptoms. Neurogenic bowel, affecting more than 75% of patients, may present with incontinence, constipation, or both and may require a colostomy if symptoms are intolerable. Sexual dysfunction is common, but often unaddressed. Men may be treated with centrally acting phosphodiesterase-5 inhibitors, although women have no similarly approved medication. Pain will affect approximately 85% of patients with MS (trigeminal neuralgia and neuropathic

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pain most commonly). Trigeminal neuralgia may be treated with carbamazepine and baclofen, while neuropathic pain may be treated with tricyclic antidepressants, anticonvulsants, or selective serotonin reuptake inhibitors. Spasticity should be treated with baclofen, although diazepam, gabapentin, or onabotulinumtoxinA may also be helpful. Treatment of fatigue, present in more than 90% of patients with MS, is multifocal and includes environmental manipulation (controlling heat and humidity levels) and energy conservation measures (napping and use of assistive devices for mobility). Amantadine has been used off-label for the pharmacological management of fatigue, but may cause insomnia and confusion [25].

Course and Prognosis

MS has an extremely varied course, characterized by two broad pathways. Primary-progressive MS is characterized by the invariable progression despite occasional plateaus or temporary minor improvements, with an average time to disability requiring use of a cane to ambulate of 6–21 years. Those diagnosed with relapsing-remitting and secondary-progressive MS tend to have an initial relapsing-remitting disease course, progressing to less prominent relapses and ensuing relentless progression. In these patients, the relapsing-remitting phase lasts for about 20 years prior to the secondary-progressive phase. The introduction of disease-modifying agents has increased the life span of a patient with MS, but is still approximately a decade shorter than expected from an age-matched general population [26].

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Part XV

The Eye

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The Red Eye

73

Gemma Kim, Tae K. Kim, and Luanne Carlson

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General Principles

Definition/Background

Red eye is one of the most common ocular conditions that presents in the primary care setting. Most cases are benign; however, some may cause permanent vision loss. Many conditions can be treated by primary care physicians. Therefore, it is important for the provider to be able to determine those cases that require urgent ophthalmic consultation. Most causes of red eye can be diagnosed by

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taking a detailed patient history and careful eye examination. Obtaining certain elements in the history can aid in determining whether an ophthalmic consultation is required. Key elements in the history include pain, decreased vision, foreign body sensation, photophobia, trauma, use of contact lens, and discharge. The assessment of clinical signs should include the location of the redness (eyelids, conjunctiva, cornea, sclera and episclera, or intraocular), unilateral or bilateral involvement, associated symptoms (pain, itching, visual decrease or loss), and other ocular (mucopurulent discharge, watering, blepharospasm, lagophthalmus) or systemic (fever, nausea) findings [1]. Equally important is to perform a thorough ophthalmologic examination, including visual acuity, penlight examination, and fundus examination.

Almost half of the eye problems presenting in the primary care setting include conjunctivitis, keratoconjunctivitis sicca, and corneal abrasions [2]. Other less common causes include episcleritis, scleritis, iritis, herpes keratitis, trichiasis, and acute angle-closure glaucoma (see Table 1).

Conjunctivitis

Acute conjunctivitis affects approximately six million people annually and consists of approximately 1% of all primary care visits in the United States [3, 4]. It is estimated that 70% of all patients with acute conjunctivitis present to primary care and urgent care centers [5]. Conjunctivitis, commonly referred to as pinkeye, is the inflammation of the mucous membrane that lines the inside surface of the eyelids and the outer surface of the eye. The causes of acute conjunctivitis can be divided into infectious (e.g., bacterial, viral, chlamydial) or noninfectious (e.g., allergic, nonallergic/irritants). The most prominent signs consist of generalized conjunctival injection with gritty discomfort, mild photophobia, and variable amounts of discharge with no loss of visual acuity [1]. Generally, viral conjunctivitis and bacterial conjunctivitis are self-limiting conditions, and serious complications are rare. Since there is no specific diagnostic test to differentiate viral from bacterial conjunctivitis, most cases are treated using broad-spectrum antibiotics [2].

Bacterial Conjunctivitis

Bacterial conjunctivitis is caused by a wide range of gram-positive and gram-negative organisms; however, gram-positive organisms are more common [6]. *Staphylococcus aureus* is more common in adults, while *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are more common in children. The incidence of *Haemophilus influenzae* has decreased as more children are immunized. Gram-negative organisms include *Escherichia coli* and *Pseudomonas* species. Hyperacute bacterial conjunctivitis is usually caused by *Neisseria gonorrhoeae* and is considered a sight-threatening infection that requires immediate ophthalmologic evaluation with hospitalization for systemic and topical therapy. It is usually transmitted from the genitalia to the hands and then to the eyes. It is characterized by a profuse purulent discharge present within 12 h of infection [7]. Additional symptoms include redness, lid swelling, and tender preauricular adenopathy. Gram staining of the purulent discharge reveals gram-negative diplococci.

History

Acute bacterial conjunctivitis initially presents with tearing and irritation in one eye but usually spreads to the opposite eye within 2–5 days. It is highly contagious and causes a rapid onset of generalized conjunctival redness, purulent discharge (yellow, white, or green), gritty discomfort, swelling of the eyelid, early morning crusting of the eyelids, and usually no loss of vision. However, one should suspect a gonococcal infection if the patient presents with profuse amounts of purulent discharge associated with a rapid progression of redness, irritation, and pain. *Neisseria gonorrhoeae* confirmed in a child should raise concern for sexual abuse. For *Neisseria meningitides*, one should consider meningitis.

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Table 1 Differential diagnosis of the red eye

	Etiology	Eye pain	Discharge	Visual acuity	Pupillary changes	Corneal involvement	Intraocular pressure	Immediate referral
Bacterial conjunctivitis	Gram + and gram - organisms	Pain with gritty sensation	Mild to moderate purulent discharge	Unchanged	None	Possible	Normal	No
Viral conjunctivitis	Adenovirus (most common)	Pain with gritty sensation	Watery	Unchanged	None	None	Normal	No
Chlamydial conjunctivitis	*Chlamydia trachomatis*	Irritated	Watery to mucopurulent	Unchanged	None	Corneal scarring with trachoma	Normal	No, unless trachoma is suspected
Allergic conjunctivitis	Environmental allergens	Gritty sensation	Watery	Unchanged	None	None	Normal	No
Keratoconjunctivitis sicca	Tear evaporation or deficiency	Irritated, gritty sensation	Watery	Fluctuating or blurry	None	Corneal ulcers and scarring in severe cases	Normal	No
Corneal abrasion/ foreign body	Trauma, chemical exposure, foreign body	Moderate to severe	Watery	Usually unchanged	None	Can cause corneal erosions, ulceration and scarring	Normal	Yes, most foreign bodies or globe involvement
Episcleritis	Idiopathic, possible association with systemic disease	Mild	Watery	Unchanged	None	None	Normal	No
Scleritis	Associated with systemic disease	Severe, constant piercing pain	Watery	Unchanged	None	None	Normal	Yes
Iritis	Infection or immune-mediated disease	Gradual onset of aching pain	Minimal and watery	Blurred	Constricted and sluggishly reactive to light	Normal	Normal	Yes

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Table 1 (continued)

	Etiology	Eye pain	Discharge	Visual acuity	Pupillary changes	Corneal involvement	Intraocular pressure	Immediate referral
Herpes keratitis	Predominantly HSV-1	Pain with foreign body sensation	Watery	Blurred	None	Recurrent infections cause reduced corneal sensation	Normal	Yes
Trichiasis	Abnormal positioning of the eyelids	Irritation	Watery	Untreated can cause vision loss	None	Can cause corneal scarring	Normal	Yes
Acute glaucoma	Narrowing of the ant. chamber	Severe throbbing	Watery	Decreased	Partially dilated, nonreactive	Swelling	Elevated	Yes

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Physical Examination

For acute bacterial conjunctivitis, visual acuity is preserved with normal pupillary reaction and absence of corneal involvement. Additional findings include conjunctival injection and swelling of the eyelid, with mild to moderate purulent discharge. Patients will often describe that their eyelids are stuck together upon wakening due to the mucopurulent discharge. For hyperacute bacterial conjunctivitis, there is chemosis (swelling of the conjunctiva) with possible corneal involvement, pseudomembrane formation, and preauricular lymphadenopathy. Patients will complain of severe pain with copious amounts of purulent discharge and diminished vision.

Laboratory Findings

In most cases of bacterial conjunctivitis, the diagnosis and the identification of the presumed organism are based on history and clinical presentation. Further studies to identify the organism and determine its sensitivity to antibiotics are reserved for more severe cases or those that are unresponsive to initial treatment [8]. If a gonococcal infection is suspected, gram staining will reveal gram-negative diplococci.

Treatment

Most cases of bacterial conjunctivitis if uncomplicated are self-limited regardless of antibiotic therapy [9]. However, antibiotics are indicated for conjunctivitis caused by gonorrhea or chlamydia and in those patients that wear contact lenses [10]. It has also been shown that antibiotics cause earlier reduction of symptoms and therefore can be prescribed. Initial preferred treatment options include erythromycin ophthalmic ointment or trimethoprim-polymyxin B drops (see Table 2). For children or for those whom it is difficult to administer eye medications, ointment is preferred as it still maintains a therapeutic effect although none may have been directly applied to the conjunctiva. Because ointment can blur the vision and cause the eyes to feel sticky, drops are recommended for adults who require clear vision for driving or work. Sulfacetamide ophthalmic drops are not considered first line due to potential allergic reactions. Fluoroquinolones are effective and well tolerated but are usually reserved for more severe infections or contact lens wearers. For those who wear contact lenses, contact lens use should be discontinued, lens case discarded, and lenses disinfected or replaced. Once antibiotics have been completed and the eye has cleared and remains free of discharge for 24 h, contact lens wear may be resumed. Bacterial conjunctivitis that is chronic, resistant to initial antibiotic treatment, or caused by gonorrhea or chlamydia requires immediate referral to an ophthalmologist.

Viral Conjunctivitis

Viral conjunctivitis is a common, self-limiting condition that is most commonly caused by adenovirus, which consists of 65–90% of viral conjunctivitis cases [11]. Other viruses which are less likely to spread include herpes simplex virus, varicella zoster virus, picornavirus (enterovirus 70, Coxsackie A24), poxvirus (molluscum contagiosum, vaccinia), and human immunodeficiency virus (HIV). Adenoviruses 8, 19, and 37 are associated with epidemic keratoconjunctivitis, which is highly contagious, while adenoviruses 3 and 7 cause pharyngoconjunctival fever which is characterized by high fevers, sore throat, and preauricular lymphadenopathy [9]. Enterovirus 70 and Coxsackie A24 cause acute hemorrhagic conjunctivitis, which is characterized by the rapid onset of painful conjunctivitis and subconjunctival hemorrhage. Although benign and resolving within 5–7 days, it can cause a poliolike paralysis developing in approximately one in 10,000 patients infected with enterovirus 70 [12]. Conjunctivitis caused by herpes simplex virus is usually unilateral with watery discharge and ipsilateral vesicular facial rash [9]. Herpes zoster virus, commonly known as shingles, can involve the eye when the first and second branches of the trigeminal nerve are involved. Ocular involvement most commonly affects the eyelids (45.8%) followed by the conjunctiva (41.1%) [13]. Herpes zoster ophthalmicus represents approximately 10–25% of all cases of herpes zoster [14].

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Table 2 Acute bacterial conjunctivitis treatment options

Medication	Dosage form	Adult dosage	Pediatric dosage	Comments
Erythromycin (Ilotycin)	0.5% ointment	Apply 1 cm ribbon up to 6×/day × 7–10 days	Apply 1 cm ribbon up to 6×/day × 7–10 days	Ointment recommended for children
Trimethoprim-polymyxin B (Polytrim)	10,000 units/1 mg/ml sol	One drop every 3 h × 7–10 days	>2 months: 1 drop every 3 h × 7–10 days	Drops better for adults
Bacitracin-polymyxin B (AK-Poly-Bac, Polycin)	500 units/10,000 units/g ointment	Apply 0.25–0.5 in. ribbon every 3–4 h × 7–10 days	Apply 0.25–0.5 in. ribbon every 3–4 h × 7–10 days	Ointment recommended for children
Sulfacetamide (Bleph-10)	10% ointment 10% solution	0.5 in. ribbon every 3–4 h and qhs × 7–10 days one to two drops every 2–3 h × 7–10 days	>2 months: 0.5 in. ribbon every 3–4 h and qhs × 7–10 days one to two drops every 2–3 h × 7–10 days	Not first line due to potential sulfa allergy
Gentamycin (Garamycin)	0.3% ointment 0.3% solution	0.5 in. ribbon bid-tid one to two drops every 4 h	>1 month: 0.5 in. ribbon bid-tid one to two drops every 4 h	May cause ocular burning
Tobramycin (Tobrex)	0.3% solution	One to two drops every 4 h	>2 months: one to two drops every 4 h	May cause ocular burning
Azithromycin (AzaSite)	1% solution	One drop bid × 2 days, then qd × 5 days	>1 year: one drop bid × 2 days, then qd × 5 days	May cause ocular burning
Ciprofloxacin (Cifloxan)	0.3% solution	One to two drops every 2 h while awake and then every 4 h while awake × 5 days	>1 year: one to two drops every 2 h while awake and then every 4 h while awake × 5 days	Reserved for severe infections or contact lens wearers
Levofloxacin (Iquix, Quixin)	0.5% solution	One to two drops every 2 h while awake and then every 4 h while awake × 5 days	>1 year: one to two drops every 2 h while awake and then every 4 h while awake × 5 days	Reserved for severe infections or contact lens wearers
Ofloxacin (Ocuflox)	0.3% solution	One to two drops every 2–4 h × 2 days and then one to two drops qid × 5 days	>1 year: one to two drops every 2–4 h × 2 days and then 1–2 drops qid × 5 days	Reserved for severe infections or contact lens wearers
Gatifloxacin (Zymar, Zymaxid)	0.5% solution	One drop every 2 h up to 8×/day × 1 day and then one drop bid-qid × 6 days	>1 year: one drop every 2 h up to 8×/day × 1 day and then 1 drop bid-qid × 6 days	Reserved for severe infections or contact lens wearers
Moxifloxacin (Vigamox, Moxeza)	0.5% solution	One drop tid × 7 days	>1 year: one drop tid × 7 days	Reserved for severe infections or contact lens wearers

History

The patient with acute viral conjunctivitis initially presents with a unilateral red eye with watery discharge and itching. Many times, the other eye becomes affected a few days later. Typically, there is absence of visual involvement or photophobia. Symptoms are typically mild with spontaneous remission in 1–2 weeks [1]. Pain, photophobia, and subconjunctival hemorrhages may be associated with keratoconjunctivitis or acute

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hemorrhagic conjunctivitis. Commonly, cases of acute viral conjunctivitis occur during or after an upper respiratory infection or with exposure to a person with an upper respiratory infection as it is highly contagious and spreads through direct contact via contaminated fingers, medical instruments, swimming pool water, or other personal items [2].

Physical Examination

For acute viral conjunctivitis, visual acuity is unaffected with normal pupillary reaction and absence of corneal involvement. Additional findings include follicular injection/erythema and swelling of the eyelid, with watery clear discharge. Keratoconjunctivitis is associated with preauricular lymphadenopathy and possible corneal infiltrates. Pharyngoconjunctivitis can be associated with subconjunctival hemorrhage. Herpes simplex virus causes a unilateral follicular conjunctivitis with an ipsilateral vesicular rash [9]. When involving the eye, herpes zoster can cause vesicular lesions in the distribution of the ophthalmic division of the trigeminal nerve with possible blepharitis, keratitis, uveitis, ophthalmoplegia, or optic neuritis [1]. Molluscum contagiosum usually presents as a unilateral follicular conjunctivitis with umbilicated lesions at the eyelid margin.

Laboratory Findings

Generally, viral conjunctivitis is diagnosed on clinical features alone. Laboratory testing is typically not necessary unless symptoms are severe, chronic, or recurrent infections or in patients who fail to respond with treatment. There are rapid immunochromatographic tests available to diagnose adenoviral infections in the office. In addition, Giemsa staining of conjunctival scrapings can aid in characterizing an inflammatory response. Fluorescein staining may reveal dendrites on the cornea for herpes simplex infections.

Treatment

As most cases of viral conjunctivitis are self-limiting and there is no effective treatment available, treatment is mostly supportive and can include cold compresses, saline rinse, ocular antihistamines, and artificial tears. These agents treat only the symptoms and not the disease itself. Antiviral medications and topical antibiotics are not indicated. Use of antibiotic eye drops can increase the risk of spreading the infection to the other eye due to contaminated droppers [11]. Treatment for ocular herpetic infections usually consists of a combination of oral antivirals and topical steroids and warrants immediate ophthalmology referral to monitor for sight-threatening corneal involvement. Molluscum treatment options include excision or cryotherapy of the lesions. Patients with molluscum do not need to be isolated from others while symptomatic [9]. If symptoms do not resolve after 7–10 days or if corneal involvement is suspected, referral to ophthalmologist is indicated.

Family and Community Issues

Patients should be counseled that since viral conjunctivitis although self-limiting is highly contagious, it is important to prevent spread by practicing strict handwashing and avoid sharing personal items with those infected. In cases of adenoviral conjunctivitis, the replicating virus is present 10 days after the appearance of symptoms in 95% of the patients but only in 5% by day 16 [8]. Due to the high risk of spread, children should be refrained from attending daycare and school for up to 1 week [9].

Chlamydial Conjunctivitis

Chlamydial conjunctivitis is a bacterial infection of the eye caused by *Chlamydia trachomatis*.. Chlamydial conjunctivitis can be divided into two types: trachoma and inclusion conjunctivitis. *Chlamydia trachomatis* serotypes A through C cause trachoma and are characterized by a severe follicular reaction which can develop into scarring of the eyelid, conjunctiva, and cornea leading to vision loss. It is the leading infectious cause of blindness worldwide [15]. It is endemic in developing countries with limited resources and is seen only sporadically in the United States. Chlamydial serotypes D through K cause inclusion conjunctivitis, which causes a unilateral chronic follicular

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conjunctivitis that usually occurs in young adults or neonates (ophthalmia neonatorum) via the birth canal from infected mothers. Chlamydial inclusion conjunctivitis is sexually transmitted from the hand to eye or from the genitalia to eye.

History

Chlamydial conjunctivitis should be suspected in sexually active patients with chronic follicular conjunctivitis that is not responsive to standard antibacterial treatment [16]. There is usually an absence of symptoms from the genital tract; however, males may have symptomatic urethritis and females may have salpingitis or chronic vaginal discharge. Ophthalmia neonatorum, also called neonatal conjunctivitis, usually occurs in the first 4 weeks of life. The incubation period is typically 7 days after delivery but can vary from 5 to 14 days if there was a premature rupture of membranes [17]. Among those neonates with known exposure to chlamydia, 30–50% will develop conjunctivitis [18].

Physical Examination

The patient usually presents with a red, mildly irritated eye with scant watery discharge to severe mucopurulent discharge with eyelid and conjunctival swelling [18]. A palpable preauricular lymph node may be present on the affected side. Vision is usually not affected, and there is usually no history of recent upper respiratory infection. Trachoma causes chronic follicular conjunctivitis that leads to entropion, trichiasis, conjunctival, and corneal scarring causing permanent vision loss.

Laboratory Findings

Diagnosis is usually made based on history and clinical presentation. However, conjunctival scrapings revealing elementary bodies via direct fluorescent antibody stain or polymerase chain reaction testing on scrapings are diagnostic. Culture of conjunctival scrapings can be performed but may take weeks to grow.

Treatment

For newborns, topical therapy is not indicated as more than 50% of affected neonates have concurrent lung, nasopharynx, and genital tract infections [10]. Recommended treatment is a systemic course of erythromycin ethylsuccinate (EryPed) 50 mg/kg/day in four divided doses per day for 14 days [19]. In order to treat inclusion conjunctivitis in adults, a systemic course of oral tetracycline (Sumycin) 250 mg four times per day for 3 weeks, erythromycin stearate (Erythrocin) 250 mg four times per day for 3 weeks, doxycycline 100 mg twice per day for 10 days, or azithromycin 1 g single dose is administered to treat the infection. Topical antibiotics may suppress the ocular symptoms but do not treat the genital disease. Pregnant patients should be treated with erythromycin since tetracyclines can cross the placenta. Sexual partners should also be treated to prevent reinfection and possible coinfection with gonorrhea should be tested.

Allergic Conjunctivitis

Allergic conjunctivitis is a type 1, IgE-mediated hypersensitivity to allergens such as pollen, animal dander, and other environmental allergens [8] and affects up to 40% of the population in the United States [20]. Seasonal allergic conjunctivitis is the most common form consisting of 90% of all allergic conjunctivitis in the United States, usually worse in the spring and summer [21]. It is often encountered in patients with atopic diseases, such as allergic rhinitis (hay fever), eczema, and asthma [22]. Perennial allergic conjunctivitis is similar to seasonal allergic conjunctivitis but occurs throughout the year, and the symptoms tend to be less severe. Other types of ocular allergies include vernal keratoconjunctivitis, atopic keratoconjunctivitis, contact allergy (contact dermatitis), and giant papillary conjunctivitis [23].

History

The hallmark for allergic conjunctivitis is itching along with watery eyes, redness, gritty discomfort, eyelid swelling, and nasal congestion. Vernal keratoconjunctivitis is more common in warmer climates and affects young patients and resolves

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by age 20. Atopic keratoconjunctivitis is the ocular version of atopic eczema or dermatitis. Contact ocular allergy is caused by contact with an allergen. Giant papillary conjunctivitis is commonly associated with contact lens use or ocular implants.

Physical Examination

Allergic conjunctivitis commonly presents with bilateral dilatation of the conjunctival blood vessels, large cobblestone papillae under the upper lid, conjunctival swelling (chemosis), and watery to mucoid discharge [1]. Redness or conjunctival injection is mild to moderate. Visual acuity is unaffected with normal pupillary reaction and absence of corneal involvement. Vernal keratoconjunctivitis is characterized by the giant papillae found under the upper eyelid. In atopic keratoconjunctivitis, the eyelid skin may have a fine sandpaper-like texture with mild to severe conjunctival injection and chemosis [23]. Giant papillary conjunctivitis may cause giant, medium, or small papillae under the upper lid similar to vernal conjunctivitis [23].

Laboratory Findings

Allergic conjunctivitis is diagnosed based primarily on history and clinical presentation. Giemsa staining of conjunctival scrapings can help characterize the inflammatory response and may reveal eosinophils. Allergy testing via direct skin testing or radioallergosorbent test (RAST) is indicated mostly for patients with systemic allergy or may be indicated for some with ocular allergy.

Treatment

Patients with allergic conjunctivitis should be advised to refrain from rubbing their eyes as this causes mast cell degranulation and worsening of their symptoms. Cool compresses may reduce eyelid swelling, and use of artificial tears throughout the day may help to clear out potential allergens. Patients should also refrain from wearing contact lenses as allergens have the ability to adhere to the contact lens surface. In addition, avoidance of known allergens may reduce exacerbations. Medical therapies that are topical include antihistamine/vasoconstrictor combination products, antihistamines with mast cell stabilizers, and glucocorticoids, which are reserved for resistant cases and should be used under the supervision of an ophthalmologist. Systemic oral antihistamines, such as loratadine (Claritin), fexofenadine (Allegra), and cetirizine (Zyrtec), are often used for the management of allergies in general; however, topical ocular medications are found to be more effective when ocular symptoms primarily predominate.

Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca or dry eye is a condition caused by decreased tear production or poor tear quality causing inadequate moisture to the eye surface. More common in adults over age 50 (women greater than men) and may be associated with underlying autoimmune disease such as rheumatoid arthritis, Sjogren's syndrome and lupus, as well as use of certain medications such as anticholinergics, antihistamines, beta-blockers and hormone replacement therapy (especially estrogen-only pills). Chronic untreated symptoms can result in corneal ulcers and permanent scarring [1, 24].

History

Common complaints of keratoconjunctivitis sicca are soreness, burning, redness, gritty discomfort, and photophobia. Sometimes excessive tearing presents (secondary to reflex secretion), and other times unable to produce tears upon crying. Dry eyes can follow trachoma, in which the lacrimal gland ducts and conjunctival goblet cells are damaged.

Physical Examination

Keratoconjunctivitis sicca often presents with mild to moderate redness or conjunctival injection with or without watery discharge. Blurred vision or partial loss may be present. Poor tear film and corneal desiccation lead to punctate lesions that are evident with fluorescein staining and blue light examination.

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Laboratory Findings

Keratoconjunctivitis sicca is diagnosed based primarily on history and clinical presentation. However, use of one or more tests may be utilized to further objectify the diagnosis including the Schirmer test, tear breakup time measurement, and tear meniscometry [2, 25]. If autoimmune disease is suspected as the underlying cause of keratoconjunctivitis sicca, serum antibody testing can be performed (e.g., rheumatoid factor [RF], antinuclear antibody [ANA], antinuclear cytoplasmic antibodies [ANCA], cyclic citrullinated peptides [anti-CCP], anti-Ro [SS-A], and anti-La [SS-B] antibodies) [24].

Treatment

Treatment is initially managed by frequent and liberal application of artificial tears such as hypromellose eye drops and ocular lubricants several times daily and at bedtime. Use of a humidifier can help to decrease tear loss in dry environments. If incomplete relief, cyclosporine eye drops (0.05%, one drop in each eye every 12 h) or lifitegrast ophthalmic solution (5%, one drop in each eye every 12 h) may be used to increase tear production in adults and adolescents greater than 16 years of age [1, 26]. Severe cases not responsive to topical therapies require referral for consideration of temporary (using plugs) or permanent (using cautery) occlusion of lacrimal canaliculi [27, 28].

Other Causes of Red Eyes

Corneal Abrasion/Corneal Foreign Body

Corneal abrasions and foreign bodies interrupt the epithelial layer of the cornea resulting in the exposure of the basement membrane. Usually due to mechanical or chemical trauma, corneal or epithelial disease (e.g., dry eye), contact lens use, or foreign body superficially adherent or embedded within the cornea. Corneal foreign bodies need to be identified and removed as soon as possible to prevent infection and ocular necrosis [2, 29]. Corneal abrasion can be a complication of trachoma secondary to constant corneal trauma of affected lashes and inadequate tears. This is the leading cause of blindness in trachoma as it often progresses to corneal erosions, ulceration, and scarring [15].

History

Patients present with usually unilateral acute onset marked tearing, redness, blepharospasm, moderate to severe pain, foreign body sensation, photophobia, and possible decreased visual acuity dependent on location of the defect along the cornea. Symptoms can be present without known trauma other than aggressive eye rubbing. Bilateral symptoms may be present when associated with chemical exposure, burns, or contact lens use. Suspicion for foreign body should be high if patient engaged in landscape, construction, or manufacturing job without the use of eye protection.

Physical Examination

Corneal disruption can be confirmed by fluorescein examination under blue light and preferably utilizing a slit lamp. Instillation of topical anesthetic (e.g., proparacaine or tetracaine) may be needed for pain control during exam. A check for foreign bodies should include under the eyelids and in the conjunctival fornices [29]. A Seidel's test should be performed if there is concern for corneal laceration or globe rupture that may not be grossly obvious. A Seidel's test is performed by placing fluorescein dye gently against the bulbar conjunctiva. In the case of a positive sign, the oozing aqueous humor at the site of penetration through the cornea appears under ultraviolet light as a "dark waterfall," clearing away excess fluorescein on the cornea. It should be noted that an in intraocular foreign body does not necessarily change visual acuity [30].

Laboratory Findings

There are no specific laboratory tests for the diagnosis of corneal abrasion or foreign body. They are primarily based on clinical history and physical examination.

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Treatment

Corneal foreign bodies require immediate removal or urgent transfer to ophthalmology. If removal performed in office, documentation of a negative Seidel's test is good practice to confirm that there was no iatrogenic penetration of the cornea during the procedure. Treatment of corneal abrasions consists of prophylactic antibiotic eye drops and/or ointment (ciprofloxacin 0.3% solution, ofloxacin 0.3% solution, erythromycin 0.5% ointment, gentamycin 0.3% ointment or solution; see Table 2) and topical pain control drops (diclofenac, 0.1% solution, one drop four times daily or ketorolac, 0.5% solution, one drop four times daily). Oral opioid analgesics (e.g., hydrocodone/acetaminophen [Vicodin], oxycodone/acetaminophen [Percocet]) can be used to relieve moderate to severe pain and have been found to allow patients to sleep more comfortably at night. All contact lens wearers, and those whose symptoms do not improve within 24 h, require immediate referral to an ophthalmology specialist [29, 30].

Episcleritis

Episcleritis is a benign inflammatory disease that affects the episclera, which is the thin layer of tissue that is beneath the conjunctiva but is superficial to the sclera. It is usually self-limiting and resolves within 3 weeks. Most cases occur mostly in young to middle-aged females but can affect any age group. The etiology is mainly idiopathic with a minority of cases associated with an underlying systemic disease, such as rheumatoid arthritis, inflammatory bowel disease, vasculitis, and systemic lupus erythematosus [31]. Episcleritis is classified into two types. In the diffuse type, the redness involves the whole episclera, whereas, in the nodular type, the redness involves a smaller contained area.

History

Patients usually present with an abrupt onset of mild eye pain, redness, watery eyes, and mild photophobia. The pain associated with episcleritis is typically mild when compared to the pain experienced with scleritis. The diffuse type of episcleritis may be less painful than the nodular type. Eye involvement may be either localized or diffuse. There is no associated discharge and vision is not affected.

Physical Examination

There is unilateral or bilateral localized or diffuse redness of the episclera. There may be mild pain with palpation. Vision is not affected and there is no edema or thinning of the sclera. A slit-lamp biomicroscope can help visualize any changes in the sclera to differentiate between episcleritis which is benign and scleritis which causes more destructive inflammation. In addition, phenylephrine eye drops can cause transient clearing of the episcleral redness so that a more careful examination of the sclera can be made.

Laboratory Findings

There are no specific laboratory tests for the diagnosis unless a systemic disease is suspected as the cause of the episcleritis. In this case, blood tests, such as rheumatoid factor, antibodies to cyclic citrullinated peptides (anti-CCP), antineutrophil cytoplasmic antibodies (ANCA), and antinuclear antibody testing (ANA), can be drawn targeted to specific inflammatory diseases.

Treatment

Since episcleritis is self-limiting and does not cause vision loss, the treatment is based on symptom relief. Treatment options include topical lubricants/artificial tears and topical glucocorticoids for severe cases [2]. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are not indicated and have been shown to have no significant benefit versus placebo [32]. Referral to ophthalmology is recommended to definitively confirm episcleritis versus scleritis and for recurrent or worsening of symptoms.

Scleritis

Scleritis is a painful and destructive inflammatory disease that affects the sclera, which comprises 90% of the outer coat of the eye. It is associated

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with an underlying systemic disorder, such as rheumatoid arthritis, Wegener's granulomatosis, and systemic lupus erythematosus, in up to 50% of patients [33]. The sclera is divided into an anterior and posterior compartment. Inflammation can occur in either compartment but rarely does it affect both. Approximately 90% of scleritis involves the anterior compartment which can be further subdivided into diffuse, nodular, and necrotizing. Diffuse anterior scleritis is the most common, least severe, and usually does not recur. Nodular anterior scleritis is the second most common and tends to be recurrent. Necrotizing anterior scleritis is the least common, most severe, and more likely to cause ocular complications. Posterior scleritis can also be subdivided into diffuse, nodular, and necrotizing but is more rare and difficult to assess clinically.

History

Patients present with a gradual onset of severe, constant, piercing pain that involves the eye and radiates to the face and periorbital region. Tenderness and redness may affect the entire eye or a more localized area. Because the extraocular muscles insert into the sclera, movement of the eye tends to exacerbate the pain. The pain is usually worse at night or in the early morning hours, causing awakening from sleep. Patients also experience headache, watery eyes, and photophobia.

Physical Examination

Examination reveals a characteristic violet-bluish hue of the globe with scleral edema and vasodilatation of the episcleral plexus and superficial vessels. The globe is usually tender to the touch. Using slit-lamp biomicroscopy, one can visualize inflamed scleral vessels which are adherent to the sclera and cannot be moved with a cotton-tipped applicator, whereas the more superficial vessels of the episclera are movable. Although phenylephrine eye drops cause blanching of the superficial episcleral vessels, the deep vessels are not affected which can aid in the differentiation between scleritis and episcleritis.

Laboratory Findings

Like episcleritis, there are no specific laboratory tests for the diagnosis of scleritis. If history and physical examination indicate a systemic inflammatory condition, specialized serologic tests can be drawn. There are some imaging studies that are useful in the evaluation of scleritis, such as ultrasonography of the orbit which can confirm scleral thickening and CT and magnetic resonance imaging of the orbit which can visualize orbital lesions associated with systemic disease processes.

Treatment

If suspected, immediate referral to ophthalmology is warranted. Two-thirds of patients with scleritis require high-dose corticosteroids or the combination of corticosteroids with an immunosuppressive agent [31]. If an underlying systemic disease is suspected or known, referral to rheumatology may be indicated.

Iritis

Iritis is the inflammation of the anterior uveal tract, also referred to as anterior uveitis. It can be caused by infection such as from a wound or corneal ulcer, or it can be caused by a systemic immune-mediated disease. Spondyloarthritides, such as ankylosing spondylitis and reactive arthritis (Reiter syndrome), are the most common systemic immune diseases associated with anterior uveitis. Uveitis can occur in up to 37% of spondyloarthropathy patients, of which most are positive for the human leukocyte antigen (HLA)-B27 allele [34, 35]. Ten to 30% of patients with juvenile idiopathic arthritis develop chronic anterior uveitis, and it remains a cause of blindness in childhood [36]. Other associated systemic diseases include sarcoidosis, inflammatory bowel disease, and Behçet's disease.

History

Patients present with a gradual onset of pain (often described as an ache) developing over hours to days with the exception of trauma. Ocular erythema and excessive tearing are commonly present. In addition, photophobia with blurred vision

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is commonly noted. Iritis can be unilateral, bilateral, or recurrent affecting either eye, dependent on the etiology or associated disease process.

Physical Examination

The eyelids, lashes, and lacrimal ducts are not involved. Conjunctival examination reveals hyperemic injection surrounding the cornea. If discharge is present, it is minimal and watery. The pupil is constricted in the affected eye and is sluggishly reactive to light. Visual acuity may be decreased in the affected eye, but extraocular movement is not affected. Both direct and consensual photophobia may be present. With slit-lamp biomicroscopy examination, keratic precipitates (white blood cells) can be visualized in the anterior chamber which is a hallmark of iritis. With severe inflammation, the leukocytes in the anterior chamber can settle and form a hypopyon, which is an accumulation of purulent material that can be visualized without magnification.

Laboratory Findings

Iritis (anterior uveitis) is diagnosed based primarily on history and clinical presentation. Slit-lamp biomicroscopy is required to properly assess the presence of leukocytes or protein accumulation in the aqueous humor within the anterior chamber of the eye. If a systemic immune-mediated disease is suspected from the patient's history and examination, diagnostic testing to confirm the specific diagnosis is warranted.

Treatment

If iritis is suspected, immediate referral to ophthalmology is warranted. Although leukocytes may be present on examination, antibiotics are not indicated. Iritis is a diagnosis of exclusion and can be associated with serious complications, such as band keratopathy, posterior synechiae, intraocular hypertension, glaucoma, cataract formation, and increased risk of herpes keratitis. If an underlying systemic disease is suspected or known, referral to rheumatology may be indicated.

Herpes Keratitis

Herpes keratitis is caused by a recurrent herpes simplex virus (HSV) infection in the cornea. It is very common in humans as both subtypes, HSV-1 and HSV-2, have humans as their only natural host. HSV-1 accounts for most oral, labial, and ocular infections and HSV-2 accounts for most genital infections. However, there is quite a bit of overlap of their distributions. HSV-1 causes over 95% of ocular HSV infections, excluding neonatal infections [37]. HSV infection is the leading cause of corneal blindness in the United States despite the fact that only a very low percentage of infected individuals develop ocular disease. Ocular HSV-1 infections are predominately unilateral; however, up to 12% of cases involve both eyes in which the infection tends to be more severe and occurs in younger individuals [38].

History

Primary HSV infection typically presents as an acute oropharyngitis type of illness. Following the initial infection, the virus may go into a latent period within any of the divisions of the trigeminal nerve. It is the reactivation of the latent HSV that causes the primary ocular infection. Patients will present with a unilateral blepharoconjunctivitis with a vesicular rash on the eyelids and follicular conjunctivitis. Patients may present with pain, photophobia, foreign body sensation, blurred vision, tearing, and conjunctival redness.

Physical Examination

Examination may reveal mild conjunctival injection with hyperemic injection surrounding the limbus (ciliary flush). After staining of the eye with fluorescein dye, the typical branching corneal ulcer (dendritic ulcer) with terminal bulbs associated with HSV infection may be seen [39]. With resolution of the infection, patients can develop subepithelial scarring and recurrent infections can lead to focal or diffuse reduction in corneal sensation.

Laboratory Findings

The diagnosis of herpes keratitis is mostly based on clinical history and examination. The dendritic

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lesions are usually pathognomonic for HSV infection. Laboratory confirmation is rarely indicated, and serologic testing is not recommended due to the prevalence of latent disease and the frequency of recurrences. In severe cases or when clinical findings are atypical, ocular scrapings of epithelial lesions can be sent for viral culture, detection of viral antigen, or detection of viral DNA.

Treatment

Treatment of herpes keratitis is dependent on whether the infection is caused by active viral replication or due to an immune response from a prior infection. Regardless, HSV keratitis warrants immediate referral to an ophthalmologist. For most cases, topical corticosteroids are not indicated as it may worsen the infection.

Trichiasis

Trichiasis is an eyelid abnormality in which the eyelashes are misdirected and grow back toward the eye causing irritation of the cornea and conjunctiva. It can be caused from congenital defects, infection, autoimmune conditions, and trauma. If left untreated, permanent scarring of the cornea can occur, leading to vision loss.

History

The history is essential in directing the clinical examination and formulation of the correct diagnosis. Important questions to ask include recent history of a severe eye infection or travel to a developing country where trachoma is commonly seen, history of herpes zoster ophthalmicus, ocular cicatricial pemphigoid (autoimmune disorder), Stevens-Johnson syndrome, eyelid surgery, or trauma.

Physical Examination

The irritation from the eyelashes causes constant eye irritation, pain, redness, excessive tearing, and sensitivity to light.

Laboratory Findings

There are no specific laboratory tests for the diagnosis of trichiasis. It is primarily based on clinical history and physical examination.

Treatment

For immediate relief, the eyelashes can be plucked out; however, regrowth usually occurs. For more severe cases or for recurrent disease, permanent removal of the affected eyelashes using a radiofrequency device, electrolysis, or cryosurgery can be performed to prevent scarring of the cornea and permanent vision loss. In some cases, corrective eyelid surgery may be indicated.

Acute Closed-Angle Glaucoma

Acute glaucoma is associated with a narrowing of the anterior chamber with obstruction of the aqueous humor from the posterior chamber to the anterior chamber of the eye. This obstruction leads to a rapid increase in intraocular pressure. Acute glaucoma is an ocular emergency and can lead to permanent blindness if left untreated. Primary angle-closure glaucoma is more common in females and those with family history. It is also more prevalent in Eskimos and Southeast Asian populations with a higher risk in individuals over 40 years of age [40]. As people age, the lens of the eye enlarges and pushes the iris forward decreasing the area where the aqueous humor drains thereby increasing the risk for angle-closure glaucoma.

History

Patients present with severe throbbing eye pain, redness, blurred vision, profuse tearing, haloes around lights (due to corneal swelling), nausea, vomiting, and headaches. In acute attacks, it is common for unilateral eye involvement and more severe symptoms. Some may experience intermittent episodes of angle closure and elevated intraocular pressure without a full-blown attack, which is referred to as subacute angle-closure glaucoma. These patients typically are asymptomatic and may experience mildly blurred vision or haloes around lights. These symptoms usually self-resolve once the angle reopens. It is important to review current medications as certain medications can cause drug-induced secondary angle-closure glaucoma.

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Physical Examination

Examination requires slit-lamp biomicroscopy which can confirm corneal edema due to the sudden elevation in intraocular pressure. There may also be dilatation of episcleral and conjunctival vessels, shallow anterior chambers, erythema surrounding the iris, and inflammatory cells within the anterior chamber. Tonometry will reveal eye pressures above 21 mmHg and may be as high as 40–80 mmHg. Gonioscopy can be performed to assess the drainage angle of the eye, and ophthalmoscopy can be used to assess the optic nerves for any damage or abnormalities.

Laboratory Findings

There are no specific laboratory tests to confirm the diagnosis of acute glaucoma. It is diagnosed based on clinical history and examination via slit-lamp biomicroscopy.

Treatment

If acute angle-closure glaucoma is suspected, immediate referral to an ophthalmologist is indicated to initiate treatment and prevent permanent vision loss. Initially medications are used to decrease intraocular pressure in preparation for laser iridotomy (treatment of choice), which creates holes in the iris so that the aqueous humor may drain freely from the posterior chamber to the anterior chamber, thereby reducing intraocular pressures.

Conclusion

There are various causes of red eye, and many may be diagnosed based on clinical history and focused examination. In the primary care setting, it is of great importance to be able to determine those cases that require immediate referral to an ophthalmologist. Indications for immediate or emergent referral include unilateral painful red eye that is associated with nausea and vomiting, severe ocular pain or visual loss in association with a red eye, corneal infiltrates or ulcers seen with fluorescein staining, and hypopyon (purulent exudate contained in the anterior chamber of the eye).

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Ocular Trauma

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T. Jason Meredith, Steven Embry, Ryan Hunter, and Benjamin Noble

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Introduction

Fifty percent of ocular trauma cases will initially present to an outpatient primary care provider's office [1]. It is imperative that family medicine physicians be able to recognize common ocular injuries, perform a thorough ophthalmologic exam, and most importantly, promptly triage these patients to improve the likelihood of vision preservation. The most frequent etiologies for eye injuries include athletic and workplace-related

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injuries, and these injuries disproportionally affect younger men [1–5]. Basketball is commonly cited as the sport with the greatest occurrence of eye injuries, and employees of manufacturing/construction companies lead the way among occupational injuries [3, 5]. Ocular trauma can lead to significant morbidity and disability, including permanent blindness, and therefore necessitates prompt evaluation and management.

This chapter aims to discuss the common yet varied forms of blunt, penetrating, and caustic eye-related traumatic injuries (Table 1). Each section will cover the pathophysiology, important history and physical exam findings, and management of these injuries.

Table 1 Categorization of ocular trauma

Blunt trauma	Caused by forceful impact, non-penetrating
Penetrating trauma	Injury with an entrance wound
Closed globe	Eyewall remains intact
Open globe	Full-thickness injury of ocular surface
Anterior segment	Involving the cornea, ant. chamber, iris or lens
Posterior segment	Involving the vitreous, retina or ocular nerve
Anterior chamber	The space between the cornea and iris

Modified from Refs. [6, 8]

Ocular Examination

A focused, systematic eye examination is essential to appropriate diagnosis of ocular trauma. The examination begins immediately upon patient contact by assessing the level of patient distress and noting any gross abnormalities with the ocular and periocular anatomy. A primary evaluation, including an abbreviated history and focused physical exam, should be completed to assess for injuries that require emergent intervention to preserve the globe and its function prior to a more generalized examination [6, 7]. This abbreviated history should focus on mechanism of injury, gross visual acuity, and whether the patient wears corrective lenses/contacts. The goal of this primary evaluation is to assess for immediate ocular emergencies such as globe rupture, large foreign body, orbital compartment syndrome, or caustic/chemical injury (Fig. 1). Once these immediate threats to the eye and its function are reasonably excluded, a more thorough history and physical exam should ensue.

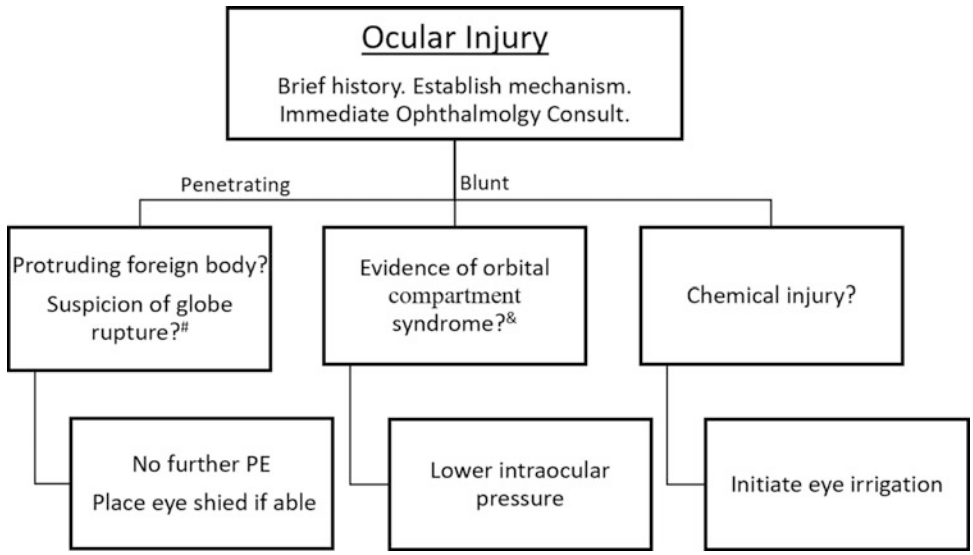


Fig. 1 True ocular emergencies. #Vitreous extrusion, a peaked or eccentric pupil, and severe subconjunctive hemorrhage. &Painful proptosis, pain with eye movements, tense orbits to palpation

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A complete ocular examination should begin with assessment of visual acuity. This simple check provides a wealth of knowledge and is the best predictor for potentially blinding conditions [4, 8]. A Snellen eye chart is the test of choice for assessing visual acuity. If the patient is unable to see the largest Snellen letters, even at close distance, then the provider may proceed by determining the ability to count fingers, detect purposeful movement, or simply whether light perception is possible [8]. Barring significant intracranial injury, reduced visual acuity should be assumed to have come from damage to the structures of the anterior or posterior segment of the eye (Table 1). Additional testing will assist in determining the location of the insult. Physicians should start with pupillary response to light and then proceed with direct evaluation with an ophthalmoscope or slit lamp.

Normal pupil reactivity is demonstrated through bilateral pupillary constriction to unilateral light exposure. Pupil reactivity is best appreciated by the "swinging flashlight test," in which the examiner alternates shining light directly into each eye and observing bilateral pupillary response. If the affected eye constricts with contralateral light exposure but is nonreactive and/or appears to actually dilate with direct light exposure as the light is shifted from the contralateral side, a relative afferent pupillary defect (RAPD) is diagnosed [8]. The presence of a RAPD is highly suggestive of an injury to the optic nerve or retina.

Following pupillary response, the gross anatomy of the anterior and posterior segments is evaluated using an ophthalmoscope or slit lamp. During this portion of the examination, mydriatics may be given to improve examination quality (Table 2).

The remainder of the examination involves assessing the periocular and superficial orbital structures including sclera, conjunctiva, eyelids, extraocular muscles, and surrounding bony orbit. While examining the six cardinal eye movements, patients should also be questioned on diplopia symptoms as this may be an indication of extraocular muscle entrapment or nerve paresis [6].

If the patient reports a foreign body sensation and the object is not immediately obvious, the eyelids should be everted for inspection. This should also prompt evaluation for a potential corneal abrasion through the use of fluorescein staining. To apply this stain, moisten the strip with saline or topical anesthetic (Table 2) and place the strip on the palpebral conjunctiva. Ask the patient to blink which will distribute the stain. Cobalt blue light, which is available on most ophthalmoscopes, can then be shone on the eye to highlight corneal irregularities.

In certain settings, radiographic procedures may be desired for further confirmation of the suspected diagnosis. Both computed tomography (CT) and ultrasound have a high degree of sensitivity and specificity for detecting many ocular abnormalities [9]. In clinical practice, the availability of CT scanners and the skill required to complete ocular ultrasound makes CT the imaging modality of choice. CT imaging is preferred

Table 2 Commonly used medications

Topical anesthetics[a]
Tetracaine 0.5%
Proparacaine hydrochloride 0.5%
Mydriatics + cycloplegics
MOA: paralyze iris sphincter (mm)
Tropicamide 0.5% or 1%
Cyclopentolate hydrochloride 0.5% or 1%
Pure mydriatics
MOA: stimulate pupillary dilator (mm)
Phenylephrine hydrochloride 2.5%[b]
Anti-inflammatories
Topical NSAIDs
(a) Diclofenac 0.1%
(b) Ketorolac 0.4%
Topical steroids should not be prescribed by family physicians
Antibiotics
Non-contact wearers:
Erythromycin 0.5%
Contact wearers[c]:
Ciprofloxacin 0.3%
Tobramycin 0.3%
Gentamicin 0.3%

Modified from Refs. [8, 10]
[a]Never prescribe! Corneal toxicity with repeated use
[b]Can be safely combined with low dose tropicamide in adults for additive effect
[c]Pseudomonas coverage

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over magnetic resonance imaging (MRI) due to cost, speed of image obtainment, and concern of metal ocular foreign body movement with MRI.

Periocular Injuries

Eyelid Lacerations

Eyelid lacerations are commonly associated with blunt or penetrating trauma, particularly in those who wear corrective lenses [4, 7]. Proper management is essential for preservation of cosmesis as well as structural function. Many eyelid lacerations will require management by an ophthalmologist. If definitive management is not immediately available, delayed closure of 24–36 h in isolated eyelid lacerations has not been shown to lead to significant complications [4, 10, 11].

When confronted with an eyelid laceration, ruling out concurrent injuries which threaten the preservation of the globe and its function must be ensured prior to addressing the laceration. History should focus on the mechanism of injury, ocular function, sensation of foreign body, and tetanus immunization status [7]. Once emergent injuries are successfully ruled out, the laceration should be carefully examined to determine its location and depth. Small superficial cutaneous wounds that do not involve the eyelid margin can be managed by primary or secondary intention and do not require referral [10]. Of note, skin adhesives are not recommended for use around the eye. Ophthalmology or plastic surgery should be involved if any of the following characteristics are present: full thickness lesions, involvement of the lid margin, proximity to the medical canthus, lacrimal duct or sac affected, or presence of ptosis signifying levator palpebrae involvement [7, 10].

Orbital Fractures

The bony orbit is comprised of the frontal, sphenoid, zygomatic, maxillary, and ethmoid bones. Fractures of these bones are common blunt trauma from motor vehicle accidents, falls, and sports-related injuries [12]. The most common type of orbital fracture is the orbital zygomatic fracture, which follows trauma to the inferolateral orbital rim. Other common fractures involve the nasoethmoid bone, orbital floor, and orbital roof, each of which are exceedingly thin. Clinical presentation will vary, and it is not uncommon for simultaneous fractures to occur [13].

Orbital rim fractures present with pain, particularly to palpation, as well as periorbital ecchymosis. Nasoethmoid fractures may also lead to subcutaneous emphysema due to sinus involvement and are a risk for medial rectus muscle entrapment [14]. Orbital floor fractures, also known as orbital "blowout fractures," commonly occur secondary to the increased intraocular pressure associated with blunt trauma. This type of fracture may classically lead to inferior rectus muscle entrapment which causes impaired upward gaze, enopthalmos (posterior globe displacement in the orbit), diplopia with ocular movements, and numbness in the infraorbital nerve distribution [15]. Since this type of fracture has sinus involvement, antibiotic prophylaxis is indicated. Oral cephalexin (250–500 mg QID for 10 days) is an appropriate choice [10].

An orbital CT scan is the test of choice for confirmation of a suspected fracture, and the physical exam should also rule out any co-occurring ocular injuries such as abrasions, hyphema, and lens or retinal injuries, as these often co-occur in many orbital fracture cases [16].

Once a fracture is diagnosed, ophthalmology should be notified. Consider involving ENT or plastic surgery based upon the location of the fracture and noted comorbid injuries. Surgical intervention is not always necessary and is decided on a case-by-case basis [16].

Subconjunctival Hemorrhage

Subconjunctival hemorrhage (SCH) is generally a self-limited condition which may be seen in patients as a consequence of repeated/prolonged Valsalva (i.e., straining in constipation, repeated emesis, childbirth), or direct trauma [17]. Although typically mild, patients who are on blood thinners or those that occur with significant ocular trauma

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may be quite striking in presentation. A protuberant conjunctiva or circumferential hemorrhage should immediately raise suspicion for occult globe rupture and be managed accordingly. SCH in infants may also be suggestive of non-accidental trauma when its onset occurs outside the peripartum period [18]. Treatment of most subconjunctival hemorrhages is supportive, as they are typically benign and resolve in a few weeks.

Open Globe Injury

An open globe injury is a full-thickness insult to the ocular surface (i.e., cornea or sclera) and is a true ocular emergency (Fig. 1). Direct penetrating injuries are the most common causes, but blunt trauma may also cause globe rupture as forces are transmitted to anatomic weak points in the eye wall (such as the limbus or the coronal equator of the globe) [19].

Open globe injuries are not always immediately apparent, and suspicion must always be maintained in the setting of trauma. Findings that suggest globe rupture include vitreous extrusion, a peaked or eccentric pupil, and severe (i.e., bullous or circumferential) subconjunctival hemorrhage. Orbital CT is the gold standard imaging modality when further evaluation is warranted, but ultrasound may also be beneficial in the hands of an experienced practitioner [20].

Patients with open globe injuries are at high risk for permanent ocular damage, extrusion/prolapse of ocular contents, and development of a post-traumatic infection of the vitreous. As such, initial management consists of minimizing increases to intraocular pressure, administering infection prophylaxis, and avoiding use of eye drops of any kind, including fluorescein and topical anesthetics. Management strategies include [21, 22]:

1. No further physical manipulation of the eye or periocular structures
2. Emergent referral to ophthalmology
3. Application of an eye shield, not an eye patch
4. Avoidance of IOP elevation:
   (a) Make the patient strict NPO status (including medications)
   (b) Elevate the head of bed >30°
   (c) Consider prophylactic intravenous antiemetics
5. Administration of empiric intravenous antibiotics. Do not use topical formulations
   (a) Vancomycin (15 mg/kg) AND ceftazidime (50 mg/kg)
6. Administration of appropriate tetanus prophylaxis

Anterior Segment Injuries

Corneal Abrasions and Non-Penetrating Foreign Bodies

Non-penetrating foreign bodies are a common presenting complaint in the primary care setting. Patient presentation likely will involve eye pain, tearing, light sensitivity and a reported foreign body sensation. If concern for penetrating injury is low, removal of a visible foreign body may be attempted. Fluorescein dye should be used to evaluate for possible corneal abrasions caused by movement of the body across the ocular surface.

Removal of non-penetrating foreign bodies should be attempted in a stepwise manner after instillation of a topical anesthetic (Table 2):

1. By irrigation with water or isotonic crystalloid
2. By retrieval with cotton-tipped applicator or similar soft contact
3. By instrumentation by an ophthalmologist

If a corneal abrasion is present, antibiotic prophylaxis should be administered to reduce the risk of infectious keratitis, whether or not foreign body removal is successful [23]. Ointment formulations, such as azithromycin, are preferred due to their additional lubricating effect. If the patient is a contact lens wearer, antibiotic selection should cover *Pseudomonas* species (Table 2).

Abrasions and other corneal injuries, when present, should be reassessed regularly with fluorescein to ensure proper healing [23]. Most defects heal gradually over 3–5 days and are

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accompanied by steady decreases to symptoms. Lesions that do not follow this pattern, the development of corneal opacities, or change in visual acuity should prompt urgent ophthalmology referral. Ocular steroids, while often used to relieve eye irritation, inhibit epithelial healing and should not be used in these patients [23]. Topical anesthetics may be used acutely during the initial evaluation; however, it is critical to never prescribe these medicines to any patient as prolonged/recurrent use is associated with permanent corneal toxicity. Systemic analgesics may be used for as needed pain relief.

Ultraviolet Light Injury

Ultraviolet (UV) light at a high enough intensity can also lead to diffuse corneal injury known as UV keratitis. Common scenarios include improper eye protection during such activities as welding (Arc Welder's Keratitis) and tanning bed use, or snow blindness secondary to prolonged UV reflection off of snowy surfaces [10, 23]. Patients typically have a delayed presentation of several hours, and the pain can be quite severe. Fluorescein staining will demonstrate diffuse superficial punctate lesions across the cornea [23]. Corneal injury secondary to UV light is treated similarly to corneal abrasions with topical antibiotics and systemic analgesics. Referral guidelines are also the same.

Traumatic Iritis and Hyphema

The force of blunt ocular trauma can lead to traumatic iritis, an acute inflammatory state in the anterior segment involving the iris and ciliary body. Patients typically present with eye pain, tearing, significant photophobia, and visual disturbances. Inspection of the eye classically demonstrates an erythematous dilation of the vessels immediately surrounding the limbus of the eye (known as ciliary flush) [8]. During pupillary assessment, the patient may report increased pain in the affected eye when light is shone in the contralateral eye. If present, this is pathognomonic for iritis [8, 10]. In the setting of trauma, if signs and symptoms of iritis are present, the clinician should also closely evaluate for a commonly co-occurring hemorrhage in the anterior chamber of the eye known as a traumatic hyphema [6].

Hyphema refers to frankly visible blood in the anterior chamber of the eye between the cornea and pupil. The etiology of traumatic hyphema formation is likely due to a sudden increase in intraocular pressure, which creates a shearing force on the vessels of the ciliary body or iris [24]. The diagnosis is made clinically by visualizing the pooling blood behind the cornea. Sitting a patient upright will facilitate blood pooling inferiorly, making hyphemas easier to detect [24].

Initial symptomatic management includes dim lighting, placing an eye shield, and elevating the head. Most hyphemas spontaneously resolve, but there is a risk of rebleed, intraocular hypertension, and corneal injury; which can lead to permanent visual impairment [25]. Therefore, once the diagnosis is made, an ophthalmology consult should ensue.

Lens Injuries

The crystalline lens is the focusing apparatus of the eye and due to its unique structure and anterior position is at high risk of injury from blunt or penetrating insult. The lens itself is encased in a transparent capsule and is suspended in place by thin zonules just posterior to the iris and anterior to the vitreous [8]. With sufficient force, the transmission of energy from blunt trauma can disrupt the protein composition of the crystalline lens and/or damage its associated structures including the lens capsule [26]. This disruption of lens proteins, or the infiltration of foreign substances secondary to capsule rupture, can lead to rapid cataract formation [26, 27]. Direct ophthalmoscopic findings, particularly with dilated eye exam, may include opacification of the lens leading to an abnormal red reflex and obscuration of fundus visualization [6, 27]. A careful dilated eye examination is also crucial to evaluate for lens subluxation/dislocation, indicative of damage to

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the filamentous zonules which suspend the lens [26, 27]. Any evidence of cataract formation or lens subluxation should prompt consultation with ophthalmology.

Posterior Segment Injuries

Retinal Detachment and Vitreous Hemorrhage

The retina is a thin neurovascular structure which lines the inside surface of the posterior globe and is responsible for transmitting visual signals to the optic nerve [8]. In blunt trauma injuries, energy transmission through the vitreous can cause a traction injury, separating the retina from its underlying structures leading to compromise of sensory input. Retinal detachment should be suspected if the patient reports new monocular flashes of light (known as photopsias) or floaters in their visual field. Patients with extensive detachment may also experience decreased visual acuity and/or demonstrate a RAPD in the affected eye [8, 28]. Definitive diagnosis is achieved through visualization of abnormal surface architecture of the retina with ophthalmoscopic examination. Ocular ultrasound is also sensitive and specific for making the diagnosis [9].

Bleeding into the vitreous of the eye may also occur following a post-traumatic retinal detachment if vascular structures are compromised. If the hemorrhage is significant, these patients will have decreased visual acuity, a RAPD, as well as a diminished or absent red reflex [8]. Regardless of the etiology, when faced with a suspected retinal detachments and/or vitreous hemorrhage, urgent referral to an ophthalmologist is indicated for definitive management. Table 3 summarizes the signs and symptoms which should prompt ophthalmology consultation discussed in this chapter.

Table 3 Signs and symptoms that warrant ophthalmology referral

Loss of vision, diplopia, or abnormal visual field	Embedded foreign body
Suspected globe rupture	Complex eyelid laceration
Painful proptosis	Hyphema
Reported flashes or floaters	Pain with ocular movements
Irregular pupil	Photophobia

Modified from Refs. [4, 27, 33]

Retrobulbar Hemorrhage and Ocular Compartment Syndrome

The bony orbit is relatively incapable of accommodating increases in intracavitary pressure. Retrobulbar hemorrhage is a rare, but potentially catastrophic complication of orbital/midface trauma. Bleeding into the retrobulbar space causes a rise in intracavitary pressure. If the pressure is great enough, it can precipitate a compartment syndrome of the orbit, which is a true ophthalmic emergency (Fig. 1). Irreversible ischemic injury can occur to the retina and optic nerve leading to monocular blindness in as little as 60 min [29].

Retrobulbar hemorrhage is a clinical diagnosis and should be suspected in all cases of facial trauma, especially if the patient has a known bleeding diathesis or is on anticoagulation. If compartment syndrome is developing, the patient will typically present with painful proptosis, pain with extraocular eye movements, decreased visual acuity, and tense orbits to palpation [29, 30]. Presence of a RAPD is an ominous sign, indicating that ischemic retinal/optic nerve damage is already developing [30]. Tonometry will confirm increased intraocular pressure (IOP >22 mmHg). If diagnosis remains uncertain, advanced imaging with CT can assist [9]. Immediate ophthalmologic surgical consultation is warranted. Until definitive surgical evaluation, management strategies to reduce swelling and IOP may improve outcomes [10, 30]:

1. Elevate head of bed to >30°
2. Make the patient NPO and consider prophylactic antiemetics
3. Methylprednisolone 125 mg IV
4. Acetazolamide 500 mg IV (avoid in sulfa allergic patients)
5. Timolol 0.5%, one drop in affected eye

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Chemical Injuries

Chemical injuries are another ocular emergency as rapid and permanent damage may ensue (Fig. 1) [31, 32]. The mainstay of treatment for all suspected chemical injuries is copious irrigation, ophthalmology consultation, and prophylactic topical antibiotic administration. Normalization of pH should only be performed with water or isotonic crystalloid. Instillation of topical analgesia should be performed if blepharospasm occurs in response to pain, in order to promote eye lid opening and enhance ease of irrigation [31]. Contact lenses should be removed if present. After irrigation for least 30 min, pH neutrality (7.0–7.3) may be assessed with a pH strip. After irritative symptoms have resolved and pH neutrality has been sustained, empiric topical antibiotics (Table 2) should be prescribed [31, 32].

Of note, alkaline exposures generally pose a greater risk to the eye, in part due to the lack of physiologic base buffering in the body [32]. Greater irrigation time may be required before pH neutrality is sustained in patients with base exposures (e.g., wet concrete, ammonia, oven cleaner, drain cleaner).

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Selected Disorders of the Eye

75

Linda J. Vorvick and Deborah L. Lam

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Presenting complaints of eye disorders need to be quickly divided into complaints that are serious and require an emergent or urgent examination and treatment and complaints that are less serious. Urgent symptoms include recent visual loss, double vision, pain, floaters, flashes, and photophobia. Less serious symptoms, which can be evaluated less urgently, include vague ocular discomfort, tearing, mucous discharge, burning, or eyelid symptoms.

The basic eye examination includes testing for visual acuity with the Snellen chart or starting at 3 years old with a picture chart or matching chart [1]. Along with visual acuity, confrontation visual fields, ocular motility testing, pupillary examination, intraocular pressure measurement, corneal staining, and ophthalmoscopy are essential elements of a complete urgent exam [2].

The Pupil

The pupil regulates the amount of light that enters the eye. Normal pupils are round, regular in shape, and nearly equal in size. The pupillary examination is designed primarily to detect neurologic abnormalities that disturb the size of the pupils. Pupillary reflexes include the direct light reflex and the indirect, or consensual, reflex, a response to light falling on the opposite eye. The measurement of pupil size in dim light assesses the motor (efferent) limb of the pupillary reflex arc; the evaluation of pupil response to direct light assesses both the motor and the sensory (afferent) limbs; the swinging light test (testing for the consensual reflex) assesses only the sensory limbs.

Constriction of the pupil to less than 2 mm is called miosis, if it does not dilate in the dark. Topical cholinergic-stimulating drops and systemic narcotics are the most frequent causes.

Dilatation of the pupil to more than 6 mm is called mydriasis, with failure to constrict to light stimulation. Topical atropine-like drops, trauma, and oculomotor nerve abnormalities are the most common causes.

Anatomic variation in the diameter of the pupil is less than 1 mm. It is best to determine this parameter in the dimmest light possible, measuring with the pupil gauge found on the near vision card. True inequality of pupil size (anisocoria) is caused by drugs, injury, inflammation, angle-closure glaucoma, ischemia, paralysis of the sphincter pupillae muscle (dilated) and dilator pupillae muscles (constricted), Horner syndrome, neuronal lesions (Argyll Robertson pupil), or, most commonly, physiologic variations [3]

The Eyelids

The eyelids protect the cornea, aid in the distribution and the elimination of tears, and limit light entering the eye. Abnormalities can occur in the skin, mucous membranes, glands, and muscles [3].

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Congenital Abnormalities

The most common congenital variation is an epicanthus, which is a vertical skinfold in the medial canthal region. This may simulate an esotropia (pseudostrabismus) [1].

Positional Abnormalities

Entropion

Entropion is the inversion of the lid margin. Etiologies are age-related (involutional), cicatricial, spastic, and congenital. Involutional entropion of aging is common, causing misdirected eyelashes (trichiasis) that irritate the eye. Secondary conditions include conjunctivitis, corneal ulcers, keratitis, and tearing. Treatment includes lubricating agents, and topical antibiotic ointment. Everting the eyelid margin away from the globe and taping can be temporary while awaiting definitive surgical procedures for symptomatic patients [4].

Ectropion

Eversion of the lid margin, or ectropion, can be age-related, cicatricial, mechanical, allergic, and congenital. Severe cases may follow Bell's palsy. Ocular manifestations include chronic conjunctivitis, keratitis, epiphora, and keratinization of the lid. Treatment options are similar to those for entropion [5].

Blepharoptosis

The etiology of blepharoptosis lies either in the innervation or the structure of the levator palpebrae superioris muscle, leading to a drooping upper eyelid and a narrow palpebral fissure. The congenital type can be unilateral or bilateral. Acquired forms include dehiscence of the levator aponeurosis, neuropathy, intracranial disorders, Horner syndrome, myotonic dystrophy, and myasthenia gravis. Surgical therapy is the only successful management strategy [6].

Inflammation

Blepharitis

Blepharitis is an inflammatory condition of the lid margin oil glands. It may be infectious, usually due to *Staphylococcus aureus*, involving the eyelash roots, glands, or both. It has been described as "acne" of the eyelids. Individuals who have acne rosacea or seborrheic dermatitis of the scalp and face are particularly vulnerable. Symptoms include swelling, redness, debris of the lid and lashes, itching, tearing, foreign body sensation, and crusting around the eyes on awakening. Management of blepharitis is primarily lid hygiene using warm compresses with baby shampoo or an eyelid cleansing agent applied with a finger, washcloth, or cotton-tipped applicators. Nightly application of bacitracin or erythromycin ointment to the lid margins is helpful when there are signs of secondary infection. For severe or recurrent cases, systemic therapy with tetracycline or doxycycline can be used for several months [7].

Hordeolum

Also known as a stye, an external hordeolum is an inflammation of the ciliary follicles or accessory glands of the anterior lid margin. It is a painful, tender, red mass near the lid margin, often with pustule formation and mild conjunctivitis. An internal hordeolum, which presents in a similar manner, involves an infection of the meibomian gland away from the lid margins. Treatment is usually simple for this self-limited condition: intermittent hot, moist compresses plus topical ophthalmic antibiotics such as tobramycin, bacitracin, erythromycin, gentamicin, or sulfacetamide to prevent infection of the surrounding lash follicles. One method to hasten drainage of the external hordeolum is to epilate (remove a hair and its root) the lash, which effectively creates a drainage channel. Occasionally an incision or puncture for drainage and administration of systemic antistaphylococcal antibiotics are necessary [8].

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Chalazion

A chalazion (lipogranuloma) is a chronic granuloma that may follow and be secondary to inflammation of a meibomian gland. During its chronic phase, it is a firm, painless nodule up to 8 mm in diameter that lies within the tarsus and over which the skin lid moves freely. It usually begins as an internal hordeolum. Asymptomatic chalazia usually resolve spontaneously within a month. Treatment options for persistent chalazia include an intralesional long-acting corticosteroid injection, which may cause hypopigmentation, or a surgical incision and curettage with a clamp [8].

Dermatitis

Dermatitis may be either infectious or of contact etiology. Contact dermatitis is common because of exposure to sensitizing irritants such as neomycin, atropine, cosmetics, lotions, soaps, nickel, thimerosal (often in artificial tears), chloramphenicol, poison ivy, and others. Manifestations include erythema, vesiculation, scaling, edema, and itching. Therapy, most importantly, is the removal of the offending agent. During the acute stages, cool compresses, antihistamines, and topical corticosteroids provide relief. Occasionally, systemic steroids are necessary such as for severe poison ivy dermatitis. The most common infectious causes are impetigo, erysipelas, and herpes zoster, with treatment the same as indicated for other locations [8].

Conjunctiva

Subconjunctival Hemorrhage

Subconjunctival hemorrhage not caused by direct ocular trauma is usually the result of a sudden increase in intrathoracic pressure, as when sneezing, coughing, or straining to evacuate. Rupture of a conjunctival blood vessel causes a bright red, sharply delineated area surrounded by normal-appearing conjunctiva (Fig. 1). The blood is located underneath the bulbar conjunctiva and gradually fades in 2 weeks. Usually no cause is found, but it is seen with hypertension, with anticoagulation, and in neonates or their mothers as a result of labor and delivery. No treatment is indicated [9].

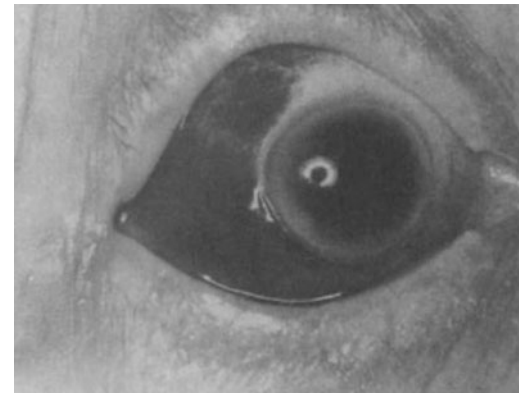


Fig. 1 Subconjunctival hemorrhage

Pingueculum and Pterygium

A pingueculum is an area of the nasal or temporal bulbar conjunctiva that contains epithelial hyperplasia, a harmless yellow-white, plaque-like thickening.

A pterygium is a triangular elevated mass consisting of vascular growth of the conjunctiva, usually nasal, that migrates onto the corneal surface. Environmental factors such as prolonged sunlight exposure and exposure to heat, wind, and dust contribute to its formation. It may be unsightly and uncomfortable, and it may interfere with vision.

Occasionally inflammatory discomfort of either a pingueculum or pterygium may require a mild topical steroid or nonsteroidal anti-inflammatory drop [3].

Surgical removal may be necessary if vision is impaired or for excessive irritation.

Recurrence may occur, but using a conjunctival autograft or amniotic membrane graft may decrease the recurrence [3, 10].

Lacrimal System

Epiphora

Epiphora is a condition in which tearing occurs because of either hypersecretion or impaired drainage of tears through the lacrimal passages. Causes

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include muscle weakness, allergy, ectropion, occlusive scarring, glaucoma, dacryocystitis, canaliculitis, and inflammation [3]. In infancy, it is usually due to congenital nasolacrimal duct obstruction, which has a high rate of spontaneous resolution during the first year. Nasolacrimal duct massage may help [1].

Dry Eye

The tear film is a complex, delicately balanced fluid composed of contributions from a series of glands. Alacrima, decreased or absent tears, occurs with keratoconjunctivitis sicca, associated with the autoimmune systemic complex of Sjogren syndrome, most frequently from rheumatoid arthritis or thyroid diseases. Other causes of dry eye can be blepharospasm, blepharitis, allergies, systemic medications, and toxins [10]. Tear film deficiency also causes nonspecific symptoms of burning, foreign body sensation, photophobia, itching, and a "gritty" sensation. Physical findings include hyperemia, loss of the usual glossy appearance of the cornea, and a convex tear meniscus less than 0.3 mm in height. Treatment is difficult and lifelong with artificial tears containing methylcellulose, polyvinyl alcohol, or 2% sodium hyaluronate four times a day to hourly. Punctal occlusion with a silicone plug or permanent punctal closure via thermal cautery can produce dramatic symptomatic improvement. Severe cases occasionally require mucolytic agents or autologous serum tears. Topical cyclosporine treatment is used in the treatment of dry eye and has shown to have clinical benefits [7, 11, 12].

Dacryocystitis

Dacryocystitis is a painful inflammation of the lacrimal sac resulting from congenital or acquired obstruction of the nasolacrimal duct. Even though congenital nasolacrimal duct obstruction occurs commonly in infants, dacryocystitis is rare and is commonly associated with nasolacrimal duct cysts. In adults, it is idiopathic or the result of an obstruction from infection, a facial trauma, or a dacryolith, rarely neoplasm. The medial lower lid location has a domed mass that is tender and painful, with discharge and tearing. Treatment includes hot packs with topical and systemic antibiotics for penicillinase-producing staphylococcal organisms. Incision and drainage may be performed for select cases; if the acute episode has resolved and is now chronic, surgical correction may be considered (dacryocystorhinostomy with silicone intubation) [8].

Dacryoadenitis

Dacryoadenitis, an enlargement of the lacrimal gland, may be granulomatous, lymphoid, or infectious in origin. If acute, this lesion is painful, tender, suppurative, and inflamed; if chronic, it may manifest simply as a swollen, hard mass. Treatment of dacryoadenitis is determined by its etiology and ranges from supportive heat therapy and massage to incision and drainage, followed by the use of systemic antibiotics and, if not responsive, by steroids [8].

Orbit

Preseptal (periorbital) and postseptal (orbital) cellulitis are bacterial infections of the periocular tissue that are serious and potentially vision threatening and lethal. Preseptal cellulitis involves only the lid structures and periorbital tissues anterior to the orbital septum. Postseptal cellulitis involves tissue behind the septum, which children and adolescents have it more commonly than adults. Routes of infection include trauma, bacteremia, upper respiratory infection, and sinusitis. Cellulitis should be considered in every patient with swelling of the eye. Critical signs include pain, fever, erythema, tenderness, swelling, and conjunctival injection. With postseptal infection, impaired ocular motility, afferent pupillary defect, proptosis, and visual loss also occur. Cavernous sinus thrombosis may develop. Leukocytosis is usually present,

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and a peripheral white blood cell count of more than 15,000/mm^3 suggests bacteremia. Computed tomography (CT) of the orbit is indicated to identify the extent of infection [8].

A bacterial pathogen is identified as the cause of periorbital cellulitis in only 30% of cases. Treatment must cover gram-positive and gram-negative anaerobes and potential methicillin-resistant *Staphylococcus aureus*. Antimicrobial therapy should be intravenous, and guidelines suggest amoxicillin/clavulanic or ceftriaxone with metronidazole as empiric treatment. Emergency consultation with hospitalization should be obtained from both an ophthalmologist and an otolaryngologist [8, 13].

Retina

Disorders of the retina often present with complaints of decreased vision. Assessing visual acuity, examining the eye, and looking for underlying medical problems are important to direct appropriate referral and care.

Arterial Occlusive Retinal Disease

Central artery occlusion (CRAO) is a severe sudden loss of vision due to an embolic or thrombotic occlusion, or obstruction, of the central retinal artery. It is usually painless and is usually monocular. Occasionally it is preceded by symptoms of amaurosis fugax, lasting 5–20 min. A cherry-red spot is often seen in the central macula. Treatment consists of immediate decompression of the eye by pharmacologic or anterior chamber paracentesis. It is important to evaluate for giant cell arteritis as this can cause a CRAO [14].

Branch retinal artery occlusion (BRAO) is a painless, less severe, more peripheral embolic phenomenon in the retinal arterial circulation, where an immediate blank or dark area is noted in the patient's visual field. It is almost always monocular. Treatment is based on finding the systemic source of the problem. Common causes include carotid plaques and cardiac valvular disease [14].

Venous Occlusive Retinal Disease

Central and branch retinal vein occlusions (CRVOs, BRVOs) must be suspected with unilateral loss of vision. A CRVO presents as a sudden loss of vision secondary to compression of the venous return by a retinal artery, causing thrombosis at that location. If an occlusion occurs at the optic nerve head, it is a CRVO; if it is seen more peripherally, it is a BRVO. The CRVO is diagnosed by the presence of flame-shaped and blot hemorrhages throughout the entire retinal field, often obscuring the view of the underlying retina (Fig. 2) [14].

A BRVO causes less severe visual loss, often not noticed by the patient. It leads to stasis of the venous flow more peripherally, which if it involves the macula causes central loss of vision. Here again, flame-shaped hemorrhages are present upon examination [14]. Treatment involves intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) therapies or laser [15].

Retinal Detachment

The annual incidence of retinal detachment is 12.9:100,000. People with high myopia and lattice degeneration of the retina have about 1% chance of a retinal detachment. Retinal detachment can occur in about 10% of patients with

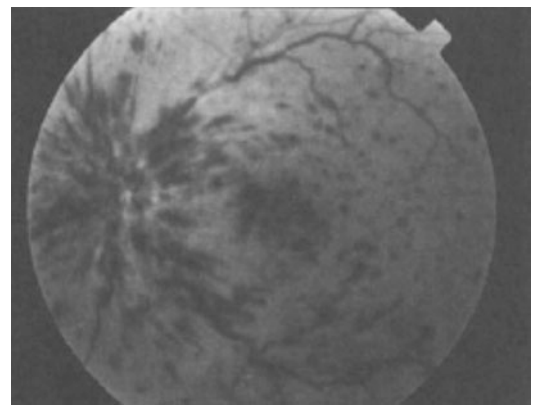


Fig. 2 Central retinal vein occlusion

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vitreous detachment which commonly occurs between the ages of 60 and 80 years. A frequent symptom of retinal detachment is a gray curtain or cloud covering a portion of the visual field. These symptoms may be preceded by a quick flash of light and a new onset of many small black floaters. On physical examination with a dilated pupil, one sees a corrugated bulbous elevation of the retina. If a detachment can be surgically repaired immediately, prior to a macular detachment, the resulting visual acuity is much better [16].

Diabetic Retinopathy

Early detection of diabetic retinopathy is important. Diabetics should have regular ophthalmologic examinations.

Nonproliferative Diabetic Retinopathy

Nonproliferative diabetic retinopathy is graded as mild, moderate, or severe. With the more severe retinopathy, cotton wool spots are present, and dot and blot hemorrhages and lipid accumulation are seen throughout the retina (Fig. 3). If there is thickening of the retina in the central macular zone, diabetic macular edema is present and can cause profound visual loss. Laser and intravitreal injections are used to stabilize and improve visual function [14, 17, 18].

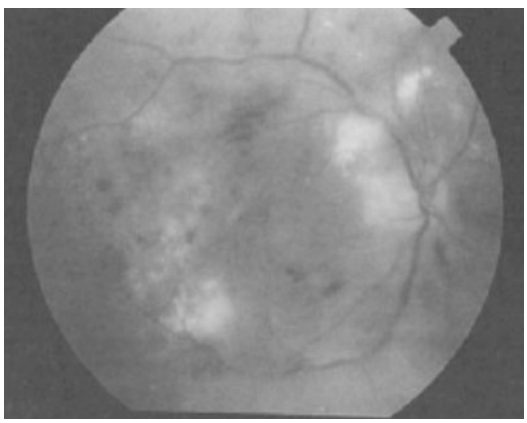


Fig. 3 Nonproliferative diabetic retinopathy

Proliferative Diabetic Retinopathy

Proliferative diabetic retinopathy is diagnosed when neovascularization is detected at the optic nerve or elsewhere in the retina. It poses a risk of retinal and vitreous hemorrhage, tractional retinal detachment, fibroglial proliferation, and retinal fibrosis. With a dilated pupil, a lacy network of fine vessels is seen, indicating retinal ischemia (Figs. 4 and 5). Panretinal photocoagulation (PRP) eliminates the mid-peripheral retina. PRP may cause some night and central vision loss but prevents progressive severe visual loss [14, 18, 19].

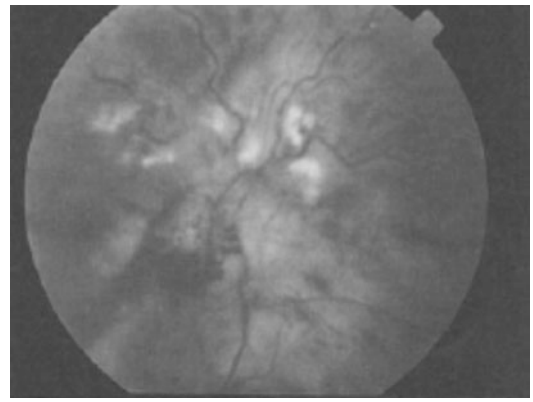


Fig. 4 Proliferative diabetic retinopathy

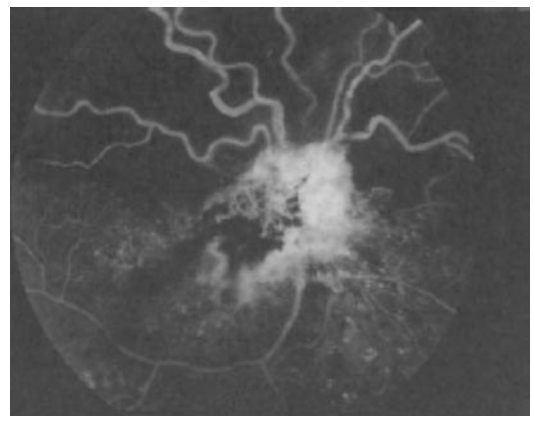


Fig. 5 Angiogram of proliferative diabetic retinopathy

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Amaurosis Fugax

Amaurosis fugax is the sudden, painless, monocular loss of vision, described as a curtain or a shade being pulled down or up, blanketing the field of vision. It totally resolves in 5–30 min. A cholesterol plaque in the carotid artery, or rarely, a calcific cardiac valvular condition, is the etiology. Treatment is directed toward anticoagulation or antiplatelet therapy. Based on the patient's risk threshold, surgical intervention, such as carotid endarterectomy or stenting, is undertaken [2].

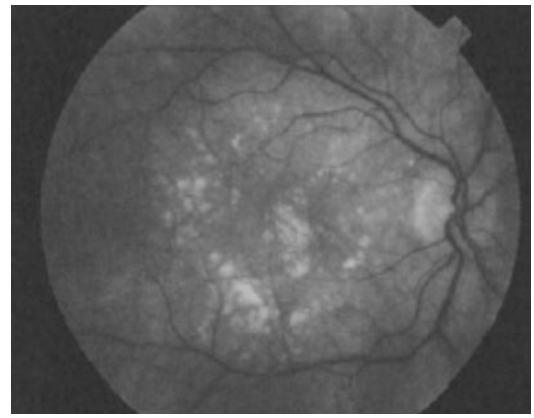


Fig. 6 Dry age-related macular degeneration

Ocular Migraine

Ocular migraine is a common condition in individuals over age 40. It presents often as a migraine aura, a fortification scotoma of jagged, multicolored lights that expand in a gradual fashion across the entire field of vision, leaving in its wake a darker or blank scotoma. Often associated with the migraine symptoms is a queasy feeling. If the episode lasts longer than 1 h, the diagnosis is in question. The eye examination at the time is entirely normal. Treatment is directed to the underlying migraine. Neuroimaging may also be considered if the symptoms are not classic or the duration exceeds 1 h [2, 14].

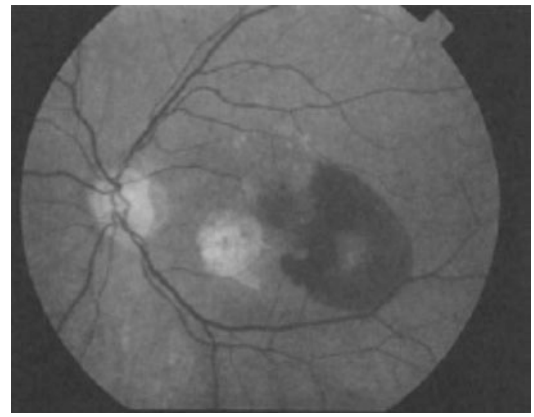


Fig. 7 Wet age-related macular degeneration

Macular Degeneration

Macular degeneration is an aging phenomenon of the inner retina that results in visual loss due to deterioration of the retinal photoreceptors. There are two types of macular degeneration: dry and wet.

Dry Age-Related Macular Degeneration

Dry age-related macular degeneration presents with slow visual loss in the central field of vision. Often the first signs are reduced reading vision and later scotoma in the central field of vision as the severity increases. There is a loss of photoreceptor function in the central macular zone (Fig. 6) [14].

Neovascular Age-Related Macular Degeneration

Neovascular age-related macular degeneration presents with sudden visual loss and hemorrhage in the central macular zone. The underlying retina develops a defect, allowing the choroidal vessels to grow through the retinal pigment epithelium (Fig. 7). The patient presents with a dark or distorted spot in the central field of vision. As the hemorrhage progresses, the vision deteriorates further. Any sudden change in vision of a patient with macular degeneration should result in immediate referral to an ophthalmologist, as neovascular age-related macular degeneration can be treated by intravitreal injection of anti-vascular endothelial growth factors or in some instances laser therapy [14, 20].

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Optic Nerve

Optic Disc Edema

Optic nerve disc edema is a common end point for several ocular disorders that result in swelling of the optic nerve head and hemorrhage in the surrounding peripapillary retina. Blood vessel margins are often blurred as they cross over the optic nerve, and splinter hemorrhages are present, distinguishing this disorder from pseudopapilledema (Fig. 8). The ocular causes of disc edema include the following: optic neuritis, anterior ischemic optic neuropathy (arteritic and nonarteritic), ischemic papillitis as in diabetes, and increased intracranial pressure. When optic disc head edema is secondary to increased intracranial pressure, it is termed papilledema. Papilledema occurs in both eyes but may be asymmetric [21, 22].

Pseudopapilledema

Pseudopapilledema is a benign, anomalous appearance of the optic nerve head due to optic disc drusen, often seen during a normal eye examination. The optic nerve head has an elevated, lumpy appearance. No nerve fiber layer edema or splinter retinal hemorrhages are seen, as would be seen with disc edema [22].

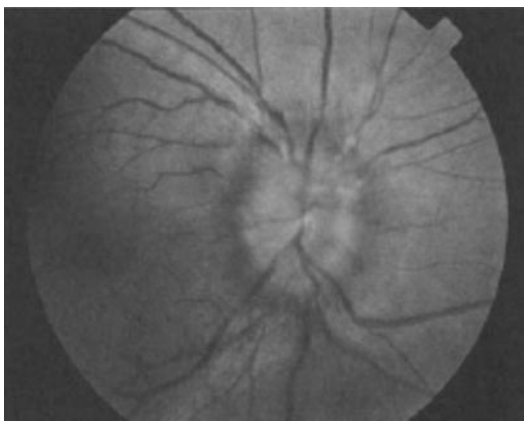


Fig. 8 Optic nerve head edema (papilledema)

Lens

Cataracts, or a clouding of the lens of the eye, are increasingly common among our aged population in the United States. The three of the more common types of cataract can be described based on the location of the lenticular opacity.

A nuclear sclerotic cataract is the hardening of the central nucleus of the lens and leads to gradual yellowing of the nucleus. With further progression, it may turn brown. Frequently this type of cataract is not appreciated at an early stage because of the gradual progression and bilateral aspect of presentation.

Cortical cataract is the whitening of the peripheral lens cortex. As the opacity progresses more centrally, more visual deprivation results. Frequently people complain of glare from lights with this type of cataract. Occasionally, double vision is noted, as cortical opacity splits light into different focal points.

Posterior subcapsular cataracts are the most visually disabling, and the progression can be rapid. Near vision is more impaired than distance vision. The disorder is often seen in patients on chronic steroids (topical or systemic) or diabetes.

The diagnosis can be easily made by dilating the pupil and using the red reflex test. Examination indicators are a hazing over with a nuclear sclerotic cataract, a spoke-like defect with a cortical cataract, and a central dark opacity with a posterior subcapsular cataract. Treatment normally is surgical, but if the patient is not a surgical candidate, chronic dilation of the pupil improves the vision in some patients. Visual recovery from surgery is frequently rapid [23].

Glaucomas

Primary Open-Angle Glaucoma

Primary open-angle glaucoma (POAG) is a relatively common disorder whose incidence increases with advancing age. There is an obstruction of aqueous outflow at the level of the trabecular meshwork. Predisposing factors include a family history of glaucoma, severe blunt trauma to the eye, and possibly high myopia. In 2018, the

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prevalence of POAG for adults 40 and older in the globally is estimated to be 3.5% [24].

Glaucoma can occur without elevated intraocular pressure. Computer-based visual field testing can be used to screen for glaucoma, but the US Preventive Services Task Force does not recommend for or is not against screening. Physical exam findings of glaucoma show damage to the optic nerve. Elevated intraocular pressure does tend to raise the risk threshold of developing glaucoma. The diagnosis is based on a triad of findings: increased intraocular pressure, optic nerve head cupping, and visual field defect. A cup/disc ratio of more than 0.60 is often a diagnostic clue, as is asymmetry between the two eyes. When a family history of glaucoma is present, or an enlarged cup-to-disc is seen, referral to an ophthalmologist is indicated (Figs. 9 and 10).

The treatment options are pharmacologic lowering of intraocular pressure, laser trabeculoplasty to attempt to increase the aqueous outflow, or surgical decompression of the eye by trabeculectomy or aqueous shunts [14, 24–27].

Angle-Closure Glaucoma

An acute angle-closure glaucoma attack is precipitated by abrupt closure in the aqueous outflow. The iris, with slight dilation, occludes the trabecular meshwork, resulting in progressively increasing pressure within the eye. The acute symptoms include pain, decreased vision, halos around lights, nausea, and vomiting. Examination reveals a cloudy or "steamy" appearance of the cornea, a nonreactive mid-dilated pupil, an area of injection around the limbus, and elevated intraocular pressure. Immediate referral to an ophthalmologist is mandatory. A laser iridotomy is often necessary, and close monitoring is needed in the uninvolved eye [27].

Oculomotor Motility

Strabismus

Strabismus is commonly defined as a deviation of the visual axis. This ocular misalignment can be found at almost any age. The malalignment of the eyes prevents binocular vision. Esotropia (in-turning of one eye) or exotropia (out-turning of one eye) are identified by examining the eyes of the newborn and children for symmetric corneal light reflex and using the cover/uncover test. At birth most infants have a small degree of exotropia that resolves during the first few months of life. Infants can reliably fix with both eyes by 4 months old. An abnormal cover/uncover test or caregiver report of deviation after 4 months old needs evaluation for potential amblyopia [1].

The treatment of strabismus is based on first correcting any refractive disorder, patching for amblyopia if present, and, lastly, surgically

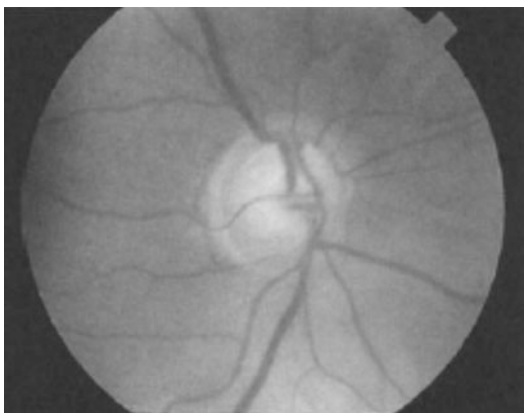


Fig. 9 Chronic open-angle glaucoma with loss of axons; note the centrally excavated optic cup

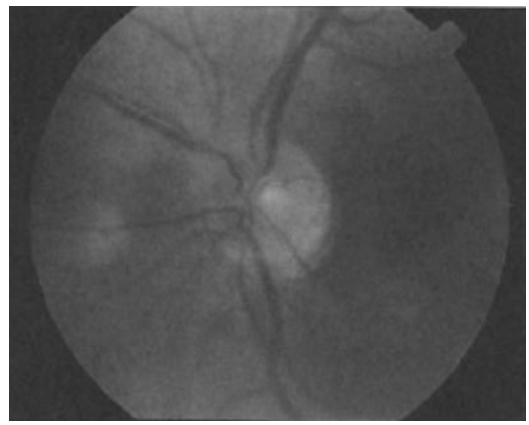


Fig. 10 Normal optic nerve with a healthy, nonexcavated optic cup

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realigning the eyes. Visual outcome is best when the problem is diagnosed early [1, 28].

Amblyopia

Amblyopia is defined as a poorly sighted eye secondary to some form of visual deprivation at an early age. Treatment is best when started at a younger age. The US Preventive Services Task Force recommends assessing visual acuity at least once between 3 and 5 years of age to detect amblyopia. Amblyopia is seen in association with strabismus and with refraction disorders [28].

Strabismus produces amblyopia by preventing image stimulation in the fovea of the deviated eye. Occasionally, the diagnosis is made using a red reflex test with a direct ophthalmic scope held about 3 feet from the child's eyes. A difference in the red reflex may indicate a refractive error, amblyopia, or an opacity in the ocular media [28].

Anisometropia is a difference in the refractive status between the eyes leading to amblyopia. Treatment of amblyopia is aimed at restoring the suppressed visual input by occluding the more favored eye with a patch, colored lenses, or pharmacologic intervention. Treatment is more successful when started under 7 years old, but older children may benefit from treatment [1, 28].

Optical Defects

Refractive Disorders

A refractive disorder occurs because the focal point of light does not fall on the retina. In addition to glasses, excimer laser surgery has produced safe and accurate correction of refractive disorders. Laser-assisted in situ keratomileusis (LASIK) is the most common refractive procedure performed today. In LASIK, the corneal stroma is remodeled with computer-controlled assistance to focus images on the retina of the eye. Recovery is usually within days to weeks. Complications, although rare, include under- and overcorrections, diffuse keratitis, and infection. Phakic intraocular lenses are an emerging option for surgical correction with very high myopia [29].

Accommodation Loss or Presbyopia

Accommodation, the ability to adjust the optic power of the eye, decreases from childhood to about age 75. In the normal human eye, as accommodation occurs, the ciliary body contracts, relaxing the zonules (or fibers) to the lens of the eye, and an active increase in lens curvature occurs, increasing the optical power of the eye. As the eye ages, hardening (sclerosis) of the lens reduces the elasticity of the lens capsule and plasticity of the lens core, resulting in a loss of accommodative amplitude. To correct this loss, reading glasses and monocular vision using contacts are prescribed. Options for surgical treatment include LASIK to achieve monovision and multifocal or accommodating intraocular lenses if cataract surgery is indicated [30].

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Part XVI

The Ear, Nose, and Throat

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Otitis Media and Externa

76

Gretchen Irwin

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Acute Otitis Media

Acute otitis media (AOM), an infection most often caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*, will affect one in four children by age 10 [1]. Differentiating the infectious AOM from the noninfectious otitis media with effusion (OME) is a critical skill for accurate diagnosis as both conditions demonstrate fluid trapped in the middle ear on physical exam.

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Epidemiology

Acute otitis media is a common diagnosis in young children. Each year in the United States, more than 2.2 million episodes of acute otitis media occur [2]. Risk factors for acute otitis media include male gender, Native American ethnicity, having multiple siblings in the home, premature birth, bottle-fed status, tobacco smoke exposure, family history of recurrent AOM, and attendance at an out-of-home day care [3, 4]. Typically, incidence peaks in the first year of life and declines after age 5 years with more than 80% of children having an acute otitis media infection before starting school [5]. Additionally, children with earlier onset of first episode of AOM may be more likely to have recurrent disease and complications leading to morbidity and mortality [4].

Diagnosis

Acute otitis media is a clinical diagnosis that should be based on history and physical exam findings. The American Academy of Pediatrics published guidelines in 2013 to help clinicians to limit over diagnosis and subsequent overtreatment of AOM. Bulging of a tympanic membrane with either associated intense erythema or recent onset of ear pain or new onset of otorrhea not explained by otitis externa are common presentations of AOM [6]. Middle ear effusion alone is not sufficient to diagnose acute otitis media, as otitis media with effusion (OME) may also present in this manner [6]. The major factor that distinguishes acute otitis media and otitis media with effusion is that OME is not an infectious process and as such there should not be signs of infection such as an erythematous tympanic membrane or otalgia.

Treatment

Treatment for AOM has been controversial in recent years as guidelines designed to promote watchful waiting in lieu of immediate antibiotic therapy often had poor adoption by physicians [7]. Current guidelines published by the American Academy of Pediatrics in 2013 emphasize the need for adequate analgesia for children during an AOM episode and offer clear definitions of children who would be most likely to benefit from observation rather than immediate antibiotic therapy. A Cochrane review of 13 randomized controlled trials that included 3401 children and 3938 episodes of acute otitis media concluded that antibiotics did not significantly reduce pain in the immediate infection phase or abnormal tympanometry findings in the long term [8]. Severe complications were rare regardless of treatment with antibiotics or watchful waiting; however, adverse effects such as vomiting, diarrhea, or rash were common with 1 child affected for every 14 children treated [8].

Analgesia

Acute otitis media is associated with significant pain that may persist for up to 7 days, despite antibiotic therapy [9]. Both oral and topical medication choices exist to alleviate pain associated with AOM. Oral ibuprofen or acetaminophen as well as topical procaine, phenazone, or benzocaine has all been shown to be effective for AOM-related pain [10, 11]. Narcotic pain medications, antihistamines, and decongestants are associated with significant side effects that outweigh any potential analgesic benefit for AOM [10, 12]. Other pain relief options may include naturopathic remedies or osteopathic manipulation though randomized controlled trials that demonstrate effectiveness of these options are limited [13, 14].

Antibiotic Therapy

All children older than 6 months with evidence of acute otitis media with otorrhea or who have severe symptoms should receive immediate antibiotic therapy [6]. Severe symptoms include toxic appearance, persistent otalgia for more than 48 h, temperature greater than 39 °C in the last 48 h, or uncertain ability to follow-up [6]. Severe bulging of the tympanic membrane may also be a sign that

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antibiotic treatment is warranted. Additionally, children less than 2 years of age with bilateral acute otitis media should receive immediate antibiotic therapy [6].

First-line antibiotic treatment for acute otitis media remains amoxicillin 80–90 mg/kg/day [3]. Currently, amoxicillin (90 mg/kg/day)-clavulanate (6.4 mg/kg/day) remains the second-line choice for antibiotic treatment of otitis media. However, new studies suggest that lower doses of clavulanate (2.85 vs. 6.4 mg/kg/day) may provide similar effectiveness with less diarrhea or diaper rash [15].

Special circumstances that may necessitate the use of an alternative antibiotic are described in Table 1.

Children less than 2 years of age should be treated for 10 days with antibiotics, while older children may be offered a 5–7-day course of therapy [6]. Any child who fails to improve after appropriate antibiotic therapy should be considered a candidate for tympanocentesis and culture of middle ear fluid to guide therapy [6].

Observation

Children who are older than 6 months with unilateral AOM without otorrhea or severe symptoms or children older than 2 years with bilateral AOM without otorrhea or severe symptoms are candidates for observation rather than immediate antibiotic therapy [6]. Severe complications are rare regardless of whether or not a child receives antibiotics [8]. No child should be offered observation as a treatment option if there is concern that the child will not be able to return for evaluation or obtain antibiotics if they fail to improve in 48–72 h of onset of symptoms [6]. As 78% of AOM episodes will resolve spontaneously and antibiotic side effects such as rash and diarrhea are common, observation in well-chosen patients is a reasonable option [17].

Table 1 When to use antibiotics other than amoxicillin for AOM [6, 16]

Special circumstance	Antibiotic choice instead of amoxicillin
Child had amoxicillin in prior 30 days	Amoxicillin-clavulanate (90 mg/kg/day amoxicillin and 6.4 mg/kg/day clavulanate)
Child has concurrent bacterial conjunctivitis	Amoxicillin-clavulanate (90 mg/kg/day amoxicillin and 6.4 mg/kg/day clavulanate)
Child has penicillin allergy	Cefdinir, cefuroxime, cefpodoxime, or ceftriaxone
Child has tympanostomy tubes in place	Topical ciprofloxacin/dexamethasone
Child on amoxicillin not improving in 48–72 h	Amoxicillin-clavulanate (90 mg/kg/day amoxicillin and 6.4 mg/kg/day clavulanate), ceftriaxone, or clindamycin

Surgical Options

Children who have more than three episodes of AOM within a 6-month period or more than four episodes of AOM within a year should be referred for evaluation for tympanostomy tubes [18]. Tympanostomy tubes may result in improved hearing initially though continued superiority to watchful waiting with respect to improved hearing is not sustained at 12–24 months [19]. Referral should focus on a careful weighing of risks and benefits of tympanostomy placement individualized for each child.

Complications

Acute otitis media can be associated with significant complications. Hearing loss may be a temporary result of fluid within the middle ear. Unfortunately, fluid may remain for weeks or months following an episode of AOM. Though hearing loss may be frustrating for both child and parents during this time, little evidence exists that speech and language delays result from this hearing loss alone [20–22]. Of note, however, rarely permanent sensorineural hearing loss may occur as a result of AOM.

Balance problems, tympanic membrane perforation, and cholesteatoma may also result from acute otitis media with recurrent episodes increasing risk [23]. Chronic suppurative otitis media, mastoiditis, petrositis, labyrinthitis, meningitis,

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abscess in the brain or epidural space or thrombosis of the lateral sinus, cavernous sinus, or carotid artery may also result from acute otitis media. Thankfully, these complications are rare. Of note, no studies have demonstrated an increase in meningitis or mastoiditis since implementation of observation guidelines in children [4].

Prevention

Effective prevention strategies would yield large benefits given the prevalence of AOM. While no targeted acute otitis media vaccine exists, introduction of higher-valent pneumococcal vaccines as well as increased influenza vaccination rates have resulted in risk reduction for AOM [24–26]. Supplementation with vitamin D and zinc has been shown to be beneficial only in children with documented nutritional deficiencies [27–29]. Xylitol, a polyol sugar alcohol found in raspberries, has been demonstrated to be effective at preventing acute otitis media though current dosing requirements of administration five times daily make its use limited [30]. Formula-fed infants may benefit from probiotics such as *Lactobacillus rhamnosus* GG, and *Bifidobacterium lactis* Bb-12 [31]. However, exclusive breastfeeding may be more beneficial as a risk reduction strategy than probiotic-supplemented formula [3]. Overall, more research into the role of probiotics is needed as early studies are promising, but limited evidence exists to identify the optimal strain, duration, dose frequency or timing of probiotic administration [32]. In infants, eliminating exposure to passive tobacco smoke and reducing pacifier use after 7 months of life may also lead to reduced incidence of AOM [3].

Otitis Externa

Otitis externa may result from infectious or allergic causes that lead to inflammation of the external auditory canal. Usually inflammation is diffuse throughout the ear canal. Three forms of otitis externa have been described, namely, acute otitis externa (AOE) which lasts for less than 6 weeks, chronic otitis externa (COE) which lasts for more than 3 months and malignant otitis externa. AOE is likely to be the result of a bacterial infection whereas COE most often results from allergy or underlying dermatologic condition [33].

Epidemiology

While the exact incidence of otitis externa is unknown, estimates suggest 10% of people will be affected at some time throughout their lives [34]. Acute otitis externa tends to occur in warm, humid climates and in individuals with narrow ear canals [33]. While children aged 7–12 may be affected, acute otitis externa is seen more commonly in adults [33]. Risk factors for disease include ear trauma such as from cotton swab use, hearing aids, and dermatologic conditions such as eczema or psoriasis. Water exposure is also a risk factor leading to the common name for AOE of swimmer's ear.

Pathophysiology

Acute otitis externa is most often caused by bacterial infection with *Pseudomonas aueriginosa* accounting for 22–62% of infections and *Staphlyococcus aureus* accounting for 11–34% of cases [35]. Polymicrobial infection is common. While only accounting for 10% of cases of acute otitis externa, infection with *Aspergillus niger* and *Candida* species has been reported after prolonged antibiotic use [33]. Polymicrobial infections have also been reported.

Cerumen provides a critical protective function in the ear by limiting exposure of skin to moisture and creating an acidic pH that is inhospitable to bacterial growth. Removal of cerumen with cotton swabs eliminates this protective barrier and creates a trauma to the ear canal that can result in infection. Similarly, water exposure can cause epithelial breakdown also leading to infection [36].

Diagnosis

Most often, patients with acute otitis externa present with symptoms of ear inflammation such as pain, itching or fullness with sudden onset

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[37]. Pain is often worsened with manipulation of the pinna or tragus. Additionally, patients may experience otorrhea, hearing loss or jaw pain [37].

Diagnosis of acute otitis externa should be made clinically with history and otoscopic examination of the affected ear. Visualization, or inability to do so, of an intact tympanic membrane is an important physical examination element to guide treatment. Findings of ear canal edema or erythema are also common. Secretions may be present and can be collected for culture, though it is not necessary to do so. Individuals who are immunocompromised or experience frequent infections may benefit from culture.

A differential diagnosis should include consideration for other infections such as perichondritis, erysipelas, otitis media with perforation and herpes zoster oticus as well as eczema, cholesteatoma and carcinoma of the external auditory canal [36].

Treatment

Acute otitis externa is best treated with pain control and topical therapies. Oral antibiotics should only be offered if the patient has poorly controlled diabetes mellitus, immunosuppression, or if the infection has spread beyond the ear canal [38]. Both antiseptic and antibiotic medications can be utilized for treatment with similar effectiveness [38].

Because there are many effective regimens, consideration of side effects, cost and dosing schedule are important when choosing a treatment strategy. For example, neomycin is effective, but ototoxic and cannot be used with a perforated eardrum. Too, neomycin may cause contact dermatitis, worsening itching, and irritation, in up to 30% of patients [39–42]. Fluoroquinolones are often preferred due to twice daily dosing and safety even if the eardrum is ruptured. However, these tend to be more expensive than other options. Some clinicians will offer ophthalmological antibiotic preparations as off label treatment for otitis externa due to cost considerations [38, 43]. Many of the combination regimens will include corticosteroids to lessen edema and hasten resolution of pain and itching [44].

Up to 20–40% of patients receive systemic antibiotics for treatment of acute otitis externa despite efficacy of topical options [20, 21]. Such treatment can increase risk of side effects and antibiotic resistance without offering improved treatment rates. Table 2 describes commonly prescribed regimens.

Regardless of medication chosen, any topical therapy will not be effective if significant cerumen is occluding the canal or if significant edema is present. Also, debris may contain exotoxins such as *Pseudomonas* exotoxin A that can promote inflammation. Gentle suction or direct visualization may be used to remove any cerumen or debris, though irrigation should be avoided in those patients who do not have an intact tympanic membrane, who are immunocompromised, or who have diabetes mellitus as an increased risk of malignant otitis externa has been reported

Table 2 Common topical preparations for acute otitis externa [45]

Component	Cost	Frequency of dosing	Comments	Ok if eardrum perforation
Acetic acid 2% solution	$	Four to six times daily	May increase pain and irritation	No
Acetic acid 2%/hydrocortisone 1% solution	$$$	Four to six times daily	May cause local irritation	No
Neomycin/polymyxin B/hydrocortisone solution	$$	Three to four times daily	Risk of contact hypersensitivity	No
Ciprofloxacin 0.2% solution	$$	BID	Single-use containers	Yes
Ciprofloxacin 0.2%/hydrocortisone 1% suspension	$$$$	BID		Yes
Ciprofloxacin 0.3%/dexamethasone 0.1% suspension	$$$$	BID		Yes
Ofloxacin 0.3% solution	$$$	Daily-BID		Yes

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[46]. An ear wick may be used with canal edema to improve drug delivery.

Topical medications should be placed into the ear with the patient lying with the affected ear up. Further, patients should be cautioned that once drops are instilled, a 3–5-min waiting period is necessary before sitting up to allow the medication to be effective [37].

Typical treatment courses are 7 days, though this may be extended to 10 days if patient is not improving. Improvement can be expected within 72 h and significant symptoms beyond 72 h should prompt reevaluation of the patient. Referral to an otolaryngologist is indicated if there is lack of expected improvement, inability to remove debris, or suspected malignant otitis externa.

Over the counter medications such as acetaminophen and ibuprofen are also helpful for pain control. Of note, benzocaine should be avoided as it can lead to contact dermatitis and worsening of symptoms. Patient should be cautioned to avoid water immersion of an affected ear until treatment is concluded. Too, hearing aids should be avoided until pain is improved.

Complications

Infection may extend to surrounding structures, causing chondritis, perichondritis, or facial cellulitis. Over time, patients with chronic infection may develop canal stenosis and conductive hearing loss.

Prevention

Episodes of acute otitis externa may be prevented by avoiding water exposure by either using well-fitting earplugs or using a hair dryer on the lowest setting to dry ears after swimming. Acetic acid 2% drops may also be helpful in acidifying the pH of the ear canal.

Chronic Otitis Externa

Chronic otitis externa is defined as acute otitis externa lasting more than 3 months or with more than four episodes per year [45]. Rather than resulting from bacterial infection, chronic otitis externa is often the result of an underlying skin condition such as atopic dermatitis or psoriasis [45]. Symptoms typically include itching and conductive hearing loss. Unlike acute otitis externa, pain is a rare finding [47]. The physical examination may show erythematous skin with either dry, scaling, or moist debris noted [47]. More than half of individuals have both ears affected [47]. Of most concern with chronic otitis externa is conductive hearing loss as well as chronic fibrosis of the canal which can make it difficult to fit hearing aids [45].

Treatment for chronic otitis externa includes removal of all irritants such as shampoo and soap as well as careful attention to keeping the ear canal dry as much as possible. Too, any underlying skin or autoimmune disease should be treated to improve the overall condition as well as the chronic otitis externa [45].

Malignant (Necrotizing) Otitis Externa

Malignant otitis externa occurs most often in elderly men with diabetes mellitus or immunosuppression [48]. Malignant otitis externa causes destruction of the external auditory canal, perichondritis, and osteomyelitis of the lateral skull base, thus early diagnosis is essential.

Symptoms of malignant otitis externa include intense, nonspecific ear pain, conductive hearing loss, and otorrhea with exam findings of granulations, polyps, or exposed bone [24]. Any individual not responding as predicted to therapy for otitis externa or with severe symptoms should be closely evaluated for malignant otitis externa. Imaging should include both fluorodeoxyglucose positron emission tomography/magnetic resonance imaging as well as high resolution computed tomography to detect osteitis before bone erosions can be appreciated [49]. Additionally, biopsy of the external auditory canal, to rule out tumor or cholesteatoma, and cultures, to guide antibiotic treatment, should be obtained.

Treatment of malignant otitis externa should include at least 4–6 weeks of antibiotics tailored to culture findings [48]. While awaiting

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sensitivities from culture specimens, empiric therapy directed against *Pseudomonas aeruginosa* is appropriate. Surgery may be needed to remove necrotic tissue.

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Disorders of the Oral Cavity

77

Nicholas Galioto and Erik Egeland

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The mouth has been described as a window to general health. Oral health can directly affect overall health and can have a significant impact on the overall quality of life of the individual patient [1]. Disease in the mouth can cause systemic disease such as endocarditis, make chronic disease management such as diabetes more difficult, or lead to adverse pregnancy outcomes [2, 3]. In addition, a thorough oral exam may provide clues to the timely diagnosis of systemic infections, immunologic diseases, hematologic conditions, and nutritional disorders [2, 3].

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Caries

Dental caries or tooth decay is the most common chronic disease worldwide [1]. Fifty percent of children between the ages of 6 and 8 years old have dental caries, and nearly 24% of adults age 24–64 have untreated dental caries [3–5]. Dental caries develops through the complex interaction of oral microorganisms (*Streptococcus mutans* and lactobacilli), metabolizing dietary sugars into lactic acid creating an acidic environment [3, 5–6]. This acidic environment leads to demineralization of the tooth's protective enamel coating and subsequent tooth decay. When the subsequent caries or decay penetrates through the full thickness of the enamel to reach the underlying dentin layer, patients will begin to typically experience mild intermittent tooth pain or sensitivity to thermal changes or sugary foods. This process is also known as reversible pulpitis and is treated through the mechanical removal of the decayed area and restoration through the placement of a dental filling [1, 4, 6]. As the demineralization process progresses, areas of dental caries may become brown or black stained making them more visible to the naked eye. If the caries goes untreated, irreversible pulpitis may ensue resulting in severe persistent dental pain despite removal of any inciting stimulus. The patient with irreversible pulpitis will often present with poorly localized pain or even pain referred to the opposite jaw [4, 6]. Once again definitive treatment involves mechanical removal of the decay through restoration, root canal or extraction by a dentist. Insufficient evidence exists in the literature to recommend antibiotic therapy, unless infection has spread to the surrounding soft tissue [4–6].

Dental exams should begin by the time patients are 1 year of age. However, the most cost-effective intervention for prevention is the public health policy of adding 0.7–1.0 parts per million of fluoride to the municipal water supply [4]. Fluoride's mechanism of action helps to strengthen tooth enamel and also has a bacteriostatic effect. Whether or not local water has been fluoridated, the effectiveness of topical fluoride has been well established. When compared with mouth rinses or gels, fluoridated toothpastes have a similar degree of effectiveness for the prevention of dental caries in children [4]. Parents should introduce tooth brushing with a smear of low-fluoride toothpaste to children as the first teeth erupt and younger than 2 years of age. Children 2–5 years of age should use a pea-sized amount of fluoride toothpaste [1]. The use of mouth rinses and gels at home is not recommended for children younger than 6 years. Tooth brushing with fluoridated toothpaste twice a day after meals is recommended as an effective way to prevent tooth decay on exposed surfaces, and flossing daily helps prevent plaque build-up on interdental surfaces. Children and adolescents should also be considered for dental sealants when they are most likely not to be compliant with daily dental hygiene regimes [1, 6]. Sealants are resinous materials that are professionally applied to the biting surfaces of teeth most susceptible to decay (molars and premolars). These sealants create a barrier against acid environments and bacterial penetration. Within the adult population, medications that decrease saliva production can be an added risk factor for carries formation [1, 3]. Additionally, dietary changes such as reducing the amount and frequency of foods with caffeine or high sugar content may further decrease dental caries rates [1, 3].

Periodontal Diseases

Periodontal disease is an inflammatory response caused mainly by bacterial colonization within the subgingival dental plaque. Though bacterial colonization is an essential component to the development of periodontal disease, certain conditions such as Down syndrome, Papillion–Lefevre syndrome, diabetes, xerostomia, medications, and smoking may further dispose a patient to periodontal disease [3, 4]. Some evidence also suggests that the presence of chronic periodontal disease may exacerbate the progression of certain diseases such as diabetes and cardiovascular disease and maybe associated with an increased incidence of preterm labor [4, 5, 7]. Periodontal disease can be divided into gingivitis and periodontitis.

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Gingivitis

Gingivitis is characterized by reversible inflammation of the gums. Patients present with erythematous swollen tender gums that bleed with routine brushing or flossing. Halitosis may also be present. Pregnancy or other hormonal changes may increase the prevalence of gingivitis in female patients [7]. Medications such as phenytoin, calcium channel blockers, and cyclosporine can also lead to increased inflammatory or non-inflammatory gingival hyperplasia [5]. Care should include removing any offending agents such as medications and tobacco and improved daily oral hygiene. General measures for treating and future prevention include improved oral hygiene with frequent tooth brushing, daily flossing, and use of warm saline or chlorhexidine gluconate 0.12% rinses [1, 4, 5]. Mouth rinses containing essential oils such as Listerine has been shown to be as effective as chlorhexidine but with less tooth staining [4, 5]. Antibiotics are not necessary unless patient presents with acute necrotizing ulcerative gingivitis also known as Vincent's disease or trench mouth [6]. Trench mouth is caused by anaerobic bacteria (*Treponema*, *Selenomonas*, *Fusobacterium*, and *Prevotella intermedia*) and typically presents in patients whose host defenses are compromised by poor oral hygiene, poor nutrition, or systemic illness. Clinically the gingival tissue is denuded with punched-out crater-like areas of necrosis and is accompanied by pain, fetid breath odor, fever, malaise, and cervical lymphadenopathy. In addition to the general measures for treating gingivitis, patients should be prescribed penicillin VK 500 mg orally every 6 h or metronidazole 500 mg orally twice daily [6]. Patients should be given a 7-day course of either regime depending on patient allergy history and/or prescriber preference.

Periodontitis

If left untreated, chronic gingivitis over a period of months to years progresses to periodontitis. Persistent exposure of the mouth to plaque-associated bacteria leads to a local and systemic inflammatory response. This inflammatory response leads to the destruction of the tooth's underlying supporting tissue and alveolar bone. Clinical presentation may demonstrate deep inflamed painful gums with deep gum pockets that bleed easily, heavy tooth plaque, receding gums with exposed root, and loose teeth. Proliferation of bacteria within the deep gum pockets can lead to periodontal abscess formation, which in addition to pain and swelling is further characterized by suppurative drainage. The most common organisms implicated in periodontitis are gram-negative bacteria such as *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and spirochetes [6]. General measures for treating periodontitis should be aggressive plaque descaling by a dentist, incision and drainage of local abscess, and good oral hygiene practices as outlined in the gingivitis section. Antibiotics are indicated when an abscess spreads to the deeper tissues of the oral cavity causing facial swelling and lymphadenopathy or if generalized periodontitis exists where the patient has multiple loose teeth [4–5]. Antibiotic regimes include doxycycline 100 mg daily, metronidazole 500 mg orally twice daily, or topical application of metronidazole, doxycycline, or minocycline [4–5]. Periodontitis is a common and serious condition affecting approximately 20% of all adults and is the leading cause of tooth loss [5]. Besides causing focal oral disease, multiple studies demonstrate an association between periodontitis and cardiovascular disease, worsening diabetes, and increased risk for preterm labor [5, 7]. However, no study has demonstrated whether treating or preventing periodontal disease leads to improved systemic disease outcomes [5].

Candidiasis

Candida species are normal inhabitants of the gastrointestinal tract and present as part of the normal oral flora in 60% of healthy adults [3, 5, 8]. Certain local and systemic factors may make certain individuals more susceptible to oral candidal infections. These include infection with

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human immunodeficiency virus (HIV), diabetes or glucose intolerance, xerostomia, malnutrition, presence of dentures, patients with cancer, medications (broad spectrum antibiotics, inhaled or systemic steroids, chemotherapy), and reduced immunity related to age [3, 5, 8]. Oral candidiasis is common in infants, affecting 1–37% of newborns [8]. Diagnosis is usually made through a history of risk factors and symptoms. The most common presentation is of painless adherent curd-like white patches along the oral mucosa and/or tongue. These white patches can be partially wiped off using a tongue blade or gauze and diagnosis confirmed either by culture or by preparing a potassium hydroxide slide looking for hyphae. Oral candidiasis may also present as erythema of the oral mucosa especially in denture wearers and/or as angular cheilitis/perleche (painful, erythematous fissures at the corners of the mouth). Common treatments include nystatin suspension 100,000 U/ml four to six times daily, Mycelex (clotrimazole) troches 10 mg five times a day, or fluconazole (Diflucan) 200 mg orally on day one then 100–200 mg daily [3, 5, 8]. Infants should be treated with nystatin suspension 0.5 ml in each cheek, massaging the cheeks to spread throughout the oral cavity. Fluconazole 6 mg/kg orally on day one and 3 mg/kg thereafter may be used as an alternative for resistant cases. All regimes are used for an average of 7–14 days [5, 8]. All pacifiers and bottle nipples should be boiled. In breastfed infants, mother's nipples may be treated if needed, with topical antifungal creams or ointment. The use of probiotics for either prophylaxis or adjunctive treatment of recurrent or primary candidiasis has shown some favorable benefit; however, further studies are needed to confirm effectives, dosages, and side effects [9].

Stomatitis

Characterized by inflammation of the mucosal lining of the mouth, lesions are erythematous, painful, and can be ulcerated. Most common conditions include hand–foot–mouth disease, herpetic stomatitis, and recurrent aphthous stomatitis/ulcers. Additional causes include herpangina, nicotinic stomatitis, and denture-related stomatitis. Any remaining causes are considered rare and uncommon. The most common forms of stomatitis present with shallow ulcerations less than 1 cm in diameter and resolve spontaneously over 10–14 days [5, 8]. Patients usually present with complaints of burning sensation, localized pain, irritation with certain foods, and intolerance to temperature changes. Recurrent aphthous ulcers or "canker sores" affects 5–21% of the population and etiology remains unclear [8]. Treatment focus is on providing topical relief. Topical agents that can be used include 2% viscous lidocaine or topical steroid such as Kenalog in Orabase applied in small amounts with a cotton swab three to four times daily. Additionally various combinations of "Magic Mouthwash" can be compounded for a swish and spit rinse three to four times daily. Suggested compounds mixed in equal parts have consisted of a thick base coating liquid such as Maalox, Mylanta, Carafate, or Nystatin mixed with, diphenhydramine, plus 2% viscous lidocaine or hydrocortisone. Caution should be noted that overuse of products containing lidocaine may cause cardiac arrhythmias. Since disease course is generally self-limited, when an ulcer persists beyond 3 weeks, other causes should be considered. Nutritional deficiencies, such as folate, B_{12}, B_6, or iron, drug reactions, Behcet's disease, Reiter's syndrome, inflammatory bowel disease, celiac sprue, lichen planus, and HIV infection have all been associated with recurrent aphthous ulcers [5, 8, 10]. Additionally, squamous cell cancer may present as a non-healing or non-resolving ulcer, and biopsy of the ulcer should be considered [5].

Lichen Planus

Lichen planus is a chronic inflammatory condition that is most likely a T cell-mediated autoimmune disease [11]. Lichen planus affects approximately 1–2% of the population, more often in those over age 40 and a slight predilection in perimenopausal women [5, 8, 12]. In women with oral lichen planus, 20% of them will also have concomitant

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involvement of the vulva and vagina [11, 12]. Patients with lichen planus have also showed a greater prevalence for exposure to hepatitis C (HCV), making it appropriate to screen patients with lichen planus for HCV infection [12]. There are four forms of oral lichen planus: reticular, atrophic, bullous, and erosive. The reticular form is the most common and manifests as asymptomatic bilateral white lace striations on the oral mucosa. The atrophic form presents as erythematous atrophic-appearing lesions within the oral mucosa and may be more painful than the reticular form. The bullous form manifests as fluid-filled vesicles, while the erosive form leads to ulcerated erythematous, painful lesions. Patients can often have a burning sensation within their mouth. Management options should start with good oral hygiene, avoiding irritating foods and tobacco products. Medium- to high-potency topical steroids are first-line therapy to treat symptomatic lichen planus [5, 12]. Clobetasol 0.05% or fluocinonide 0.05% is applied twice daily to lesions [11, 12]. Patients with widespread oral disease or diffuse ulcerations may not adequately respond to corticosteroids alone. Topical calcineurin inhibitors such as pimecrolimus 1% (Elidel) or tacrolimus 0.1% (Protopic) or topical retinoids can be effective second line or adjunctive forms of therapy for these patients [11, 12]. Patients refractory to standard topical therapies may have using oral retinoids such as alitretinoin [13].

Glossitis

Geographic tongue also known as known as benign migratory glossitis affects 1–14% of the population and is of unknown etiology [14, 15]. Geographic tongue is characterized by areas of papillary atrophy that appear smooth and are surrounded by raised wavy borders. The regions of atrophy spontaneously resolve and migrate giving the tongue a topographic map appearance. The condition is benign, but some patients may have sensitivity to hot or spicy foods. Treatment for symptomatic patients may include bland foods, use of topical steroids triamcinolone 0.1% (Oralone) or antihistamine mouth rinses which can also be used to help reduce tongue sensitivity [14, 15].

In fissured tongue, deep groves develop within the tongue usually due to the physiologic deepening of normal tongue fissures secondary to aging. The deeper fissures can lead to food trapping causing inflammation of the tongue and halitosis. Gentle brushing of the tongue is useful in symptomatic patients. Down's syndrome, Sjogren syndrome, Melkersson–Rosenthal syndrome, psoriasis, and geographic tongue have all been associated with fissured tongue [14].

Hairy tongue results from the accumulation of keratin on the filiform papillae of the dorsal tongue leading to hypertrophy of the papillae. The hypertrophied papillae tend to resemble elongated hairs. Bacteria and debris get trapped in the elongated hairs causing discoloration of the tongue. Color of the tongue can range from white to tan to black. This condition is most often associated with smoking, poor oral hygiene, and antibiotic use [4, 14, 16]. Most patients are asymptomatic but some may experience halitosis or abnormal taste. Daily debridement with a soft toothbrush or tongue scrapper can remove the keratinized tissue.

Oral hairy leukoplakia is characterized by white hairy-appearing lesions on the lateral borders of the tongue either in a unilateral or bilateral fashion. This condition is associated with Epstein–Barr super infection or immunocompromised condition [14, 16]. In the absence of a known immunocompromised condition, testing for human immunodeficiency virus (HIV) should be considered. Treatment consists of the use of antiviral medications though recurrences are common. Acyclovir (Zovirax) 800 mg orally five times daily or ganciclovir 100 mg orally three times a day for 1–3 weeks may be used [14].

Atrophic glossitis results from the atrophy of the filiform papillae and is also referred to as smooth tongue. The tongue has a smooth glossy appearance with a red or pink background, and the patient will often complain of a painful sensation within the tongue. Atrophic glossitis is most commonly caused by nutritional deficiencies [14]. Nutritional deficiencies of iron, folic acid,

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riboflavin, niacin, and B_{12} are most often implicated [14]. Other possible etiologies include syphilis, candidal infection, amyloidosis, celiac disease, Sjogren syndrome, protein malnutrition, and xerostomia [14].

Halitosis

Halitosis is an unpleasant or offensive odor emanating from the oral cavity. In approximately 80% of the cases, halitosis is caused by conditions of the oral cavity [17]. The most likely cause of oral malodor is the accumulation of food debris and bacterial plaque along the teeth and tongue. The oral malodor arises from the microbial degradation of these organic substrates into volatile sulfur-containing gas compounds. Though the majority of cases of halitosis originate in the oral cavity, non-oral etiologies may include infections of the upper or lower respiratory tract, metabolic disturbances, carcinomas, systemic diseases, and medications [17]. Therefore, before halitosis can be managed effectively, an accurate diagnosis must be made. Achieving an accurate diagnosis starts with first determining whether the source of the odor is of an oral or non-oral etiology. One of the simplest ways to distinguish oral from non-oral etiologies is to compare the smell coming from the patient's mouth with that exiting the nose. To perform this sniff test, have the patient tightly hold their lips together and forcibly blow air through the nostrils. Repeat the test with the patient holding their nostrils closed and passively breathing through their mouth. One can then compare the odors emanating from each cavity and further characterize the intensity and quality of the odor. A systemic origin may be suspected in the case where the odor from the mouth and nose are of the same intensity and quality [18].

As noted, the majority of cases of halitosis originate from the oral cavity. The oral cavity should be inspected for evidence of gingivitis, periodontal disease, and oral cancers. All of which can produce foul putrid-smelling breath. In patients where a rigorous oral hygiene regime of twice daily brushing, flossing, and professional cleaning does not improve the problem, the tongue especially the posterior region should be suspected [17, 18]. The posterior tongue can be assessed by obtaining a gentle scrapping of the area using a plastic spoon. The spoon can be smelled to compare the odor with the overall mouth odor [17]. Gentle but thorough tongue cleaning using either a tongue scrapper or toothbrush should be added to the daily oral hygiene routine. Faulty dental restorations or dentures can be another etiology of bad breath. The odor from dentures may have a somewhat sweet though unpleasant nature and can be more easily identified when the dentures are placed in a sealed plastic bag and smelled after a few minutes [17]. Saliva also affects bad breath. Xerostomia or dry mouth may be a contributor to halitosis secondary to decreased salivary flow and the resultant increased risk for dental infections. A transient odor associated with acute tonsillitis is common especially in children. Tonsillectomy, however, is rarely indicated for chronic halitosis [17, 18].

Nasal sources are second in frequency to oral etiologies as causes of halitosis [17, 18]. Nasal odor is often indicative of sinus infection, but may also signal an obstruction to normal air flow that could occur with nasal polyps, craniofacial anomalies, or foreign body (especially in small children). Nasal discharge can have a fetid cheesy odor [17]. The lungs are also a source of some odors secondary to infection and/or metabolic disorders. A pulmonary source is suggested when the odor intensity increases during expiration. Lung abscess, necrotic tumors, tuberculosis, and bronchiectasis are all possible infections causing bad breath. Because of the associated pus production and tissue necrosis with these diseases, a putrid foul odor similar to rotting meat is produced [17]. Hepatic failure, renal failure, and diabetes are all systemic diseases that may contribute to or present as halitosis. Hepatic failure or cirrhosis may have a mousy, musty, or rotten egg smell, while the uremia from kidney failure can impart a fishy ammonia-type smell to the breath [17]. Trimethylaminuria is a rare genetic metabolic condition that can also produce a foul fishy odor [17, 18]. Diabetes is best known for its distinct sweet fruity odor [17]. GI causes are rarely implicated, though some sources have reported halitosis can be intensified or aggravated by the presence of a *Helicobacter pylori* (*H. pylori*) infection

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[17, 19]. *H. pylori* is thought to contribute to the development of halitosis by increasing the production of volatile sulfur compounds (VSC). Reduction or elimination of *H. pylori* in patients with antibacterial therapy therefore may have in the indirect consequence of improving halitosis symptoms by decreasing overall VSC production [19]. Probiotic studies using Lactobacillus strains have not shown clear and definitive benefits in the management of halitosis [20].

Temporomandibular Disorders

Temporomandibular joint (TMJ) disorders are a constellation of conditions characterized by pain and/or dysfunction of the TMJ and surrounding tissues. Incidence is approximately 15% in the general population, although a much smaller percentage seeks medical care for their symptoms [21] TMJ disorders are thought to be three to four times more common in women, with onset of symptoms usually in the first half of life [21]. In most cases, these disorders lack organic pathology, are self-limited, and resolve spontaneously [21–22]. Underlying causes of TMJ disorders and treatment options are poorly understood. Behavioral, psychological, and structural factors all appear to contribute to the formation of TMJ disorders. The diagnosis of TMJ disorders is based largely on history and physical examination [21]. Patients complain of pain, clicking or popping of the jaw, and occasionally limited range of motion. Pain severity is often poorly correlated with the degree or presence of organic pathology. Examination may reveal tenderness of the TMJ and/or muscles of mastication. Occasionally there is palpable crepitus or audible clicks; however, these findings are also commonly found in asymptomatic individuals as well. Based on clinical findings, TMJ disorders are divided into intra-articular or extra-articular (involving muscles of mastication) categories [21]. The differential diagnosis of TMJ disorders should include, but not limited to, dental caries/abscess, oral lesions/ulcerations, osteoarthritis, rheumatoid arthritis, temporal arteritis, and claudication of the masticatory muscles [21, 22]. Oral habits such as frequent gum chewing or bruxism may aggravate symptoms or cause inflammation within the joint. Imaging is rarely useful in the diagnosis of TMJ disorders, since most symptoms are self-limited and should be reserved for patients with persistent symptoms where conservative therapy has failed or internal joint derangement is suspected from degenerative articular disease, fracture, or dislocation. To screen for organic pathology, the panoramic radiograph is the preferred initial study [21, 22]. More advanced imaging such as ultrasound, CT or MRI should be ordered based on the findings of the panoramic film. Patient education should be at the forefront of treating nonorganic and chronic TMJ disorders [21, 22]. It is important for patients to understand that TMJ is generally not related to oral pathology and these disorders are self-limiting and nonprogressive in the absence of any systemic disease. The mainstay and most common dental treatment for TMJ has been dental splinting or interocclusal orthosis. Dental splints work to primarily open the mouth, release muscle tension, and prevent teeth clenching or grinding [21, 22]. Generally most patients perceive the splint to be effective in providing symptomatic improvement. Cognitive behavioral therapy, muscle relaxation techniques, biofeedback, physical therapy, and acupuncture have all shown to be helpful in at least temporarily reducing the pain associated with TMJ [21, 22]. Nonsteroidal anti-inflammatory agents are frequently utilized as first-line pain medications. Other medications to be considered include corticosteroids, muscle relaxants, antiepileptics, anxiolytics, and tricyclic antidepressants. Caution should be used in utilizing selective serotonin or serotonin-norepinephrine reuptake inhibitors, as these medications can induce bruxism [21, 22]. Botox may be effective in treating TMJ disorders, but current evidence is inconclusive [21]. Referral for surgical evaluation is rarely indicated in the absence of organic pathology [21, 22].

Oral Cancer

Cancers of the oral cavity and oropharynx are the ninth most common cancer in the United States [23]. African-Americans have a higher incidence than Caucasians, and males have a slight predominance over their female counterparts [23]. Patients are typically over age 40 at time of

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presentation. Squamous cell carcinomas account for approximately 90% of all oral cancers [5, 23, 24]. Oral cancers most commonly occur on the anterior two-thirds of the tongue, floor of the mouth, hard palate, buccal mucosa, and vermillion border of the lower lip [24]. The major risk factors for developing oral cancer are tobacco use of any kind and heavy alcohol consumption [5, 23]. Over 75% of all head and neck cancers are linked to one or both of these risk factors, and there does appear to be a synergistic effect when the two are used concomitantly [5]. Despite decreased smoking rates over recent years, the incidence of oropharyngeal cancers have continued to rise while those of oral cancers have decreased [24]. Oropharyngeal cancers include those found on the posterior one-third of the tongue, soft palate, or tonsils [24]. The increased incidence of oropharyngeal cancers is largely explained by the rise in human papillomavirus (HPV)-positive cancers [24–25]. The vast majority of HPV-related oropharyngeal cancers is caused by HPV-16 [25]. These cancers tend to occur more frequently in middle-aged Caucasian males with sexual behavior as the main risk factor [25]. Other potential risk factors for oral and oropharyngeal cancers include ultraviolet light exposure, history of previous head and neck radiation, HIV, and chronic mechanical irritation from poor fitting dentures or restorations. Overall 5-year survival rate for oral cancer is 50–55%, but if detected at an early stage, survival rates can approach 90% [5]. HPV-related oral cancers tend to have better survival rates and lower rates of recurrence [5, 25]. Oral cancers can be subtle and asymptomatic in the early stages and may present as a solitary chronic ulceration, red or white lesion, indurated lump, fissure, or enlarged cervical lymph node. Other concerning symptoms include bleeding, unexplained mouth or ear pain, odynophagia, chronic sore throat, or hoarseness. Oral leukoplakia is the most commonly known premalignant lesion and is defined as a white patch or plaque that cannot be explained by another clinical cause [5, 23]. Similar red lesions are called erythroplakia, and combined red and white lesions are known as speckled leukoplakia or erythroleukoplakia. Erythroplakia and erythroleukoplakia are more likely than leukoplakia to microscopically demonstrate dysplastic or cancerous changes [23]. Any abnormality, ulcer, white, red, or mixed lesion that is not resolving in 3–4 weeks, especially after removing any irritating precipitant such as tobacco, alcohol, and ill-fitting dental restorations, should be considered for biopsy to exclude malignancy [5, 23]. Treatment generally involves surgery and/or radiation therapy. Radiation therapy and/or chemotherapy can be used for patients not amenable to surgery or palliation for unresectable tumors. Counseling of patients regarding risk factors (tobacco, alcohol, sun exposure, and sexual habits) and providing HPV vaccination to adolescent patients can help reduce the future incidence of oral cancers [25]. The American Cancer Society recommends that adults 20 years or older have thorough oral cavity exams as part of any cancer-related check-up [24]. The United States Preventive Services Task Force has found inadequate evidence to make any similar recommendation [24].

Other Oral Lesions

Bony Tori

Tori are benign, non-neoplastic bony protuberances that arise from the cortical plate. They are more common along the hard palate of the mouth but can also arise from the floor of the mouth. Those that form along the hard palate are known as palatal torus or torus palatines, while those located along the lingual aspect of the mandible are known as mandibular torus or torus mandibularis. The overall prevalence in the general population is 3%; palatal tori are three to four times more common than mandible tori [5, 23]. These lesions are thought to be congenital anomalies though they usually do not develop until adulthood. They can be confused for cancerous growths. Bony tori are usually painless and do not cause any symptoms. No management is necessary; unless the tori are interfering with oral function, denture fabrication, or subject to recurrent traumatic ulceration, then surgical removal by an oral surgeon is recommended [5, 23].

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Mucocele

Mucoceles are benign fluid-filled sacs which result from disruption of a salivary gland duct with extravasation of mucus into the surrounding tissue, usually secondary to mild local trauma such as biting [26]. Most frequently they occur on the lower lip and are more prevalent in children and young adults [23, 26]. Patients typically present with a pinkish/blue dome-shaped fluctuant papule or nodule. The underlying gelatinous sac can often be felt with palpation. Patients are seldom symptomatic, but often find the lesions irritating because of the recurrent trauma that occurs while eating. Lesions will often resolve on their own due to spontaneous rupture. If the lesion becomes symptomatic, it can be excised, which should include the entire cyst to prevent recurrence. Once excised, the specimen should be sent for pathologic examination to rule out neoplastic changes [5, 23]. As with any lesion in the mouth that does not resolve on its own within 3–4 weeks, consideration should be given for further assessment and pathologic examination either by biopsy or excision [5].

Pyogenic Granuloma

A pyogenic granuloma or lobular capillary hemangioma is an acquired benign vascular growth on the skin and mucous membranes, occurring more often in children and young adults [27]. Pyogenic granulomas appear as erythematous rapidly growing lesions which develop in response to local irritation, trauma, immunosuppression, or increased hormone levels related to pregnancy [7, 23]. These lesions may be smooth or lobulated, easily bleed when touched, and are non-painful. Oral pyogenic granulomas vary in size and most often develop along the gingival border, but can be found anywhere within the oral mucosa. Treatment is generally necessitated by the risk for recurrent bleeding, ulceration, cosmetic concerns, and the low likelihood of spontaneous regression. Options for treatment include surgical excision, laser therapy, systemic or topical therapies, especially beta-blockers [27–29]. Recurrence is uncommon but can be as high as 15% [29]. Pyogenic granulomas induced by pregnancy, however, are more likely to reoccur due to the associated hormonal changes, but are also more likely to spontaneously resolve following childbirth. Therefore observation alone may be an adequate treatment in this patient population [7, 23].

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Selected Disorders of the Ear, Nose, and Throat

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Jamie L. Krassow, Justin J. Chin, Angelique S. Forrester, Jason J. Hofstede, and Bonnie G. Nolan

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Adult Hearing Loss

General Principles

Hearing impairment affects over 30 million people in the United States and is the fourth leading cause of disability worldwide [1, 2]. As hearing loss is primarily associated with increasing age, its prevalence is expected to rise with an aging population [2]. Hearing loss can significantly degrade quality of life and physical function and has been associated with cognitive decline, dementia, and depression [3, 4].

Pathophysiology

There are three different types of hearing loss: adult – (1) conductive hearing loss, (2) sensorineural hearing loss, and (3) mixed conductive and sensorineural hearing loss.

Conductive hearing loss is secondary to anomalies of the outer or middle ear, which may be due to obstruction of the external auditory canal, impairment of the tympanic membrane function, or middle ear pathology [1, 2]. Examples of conditions that cause conductive hearing loss include (but are not limited to) cerumen impaction, foreign body in the auditory canal, otitis externa or media, exostoses or osteomas of the external auditory canal, tympanic membrane perforation, tympanosclerosis, cholesteatoma, and otosclerosis [1].

Sensorineural hearing loss is due to dysfunction of the inner ear or neural pathways to the auditory cortex. Age-related hearing loss, or presbycusis, is the most common type of sensorineural hearing loss and usually affects high frequencies before progressing to lower frequencies [1, 2]. Noise exposure due to occupational, recreational, or accidental noise also results in sensorineural hearing loss. Prolonged and chronic

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noise exposure to levels of greater than 85 dB or sudden noise exposure of greater than 130 dB can lead to permanent and irreversible hearing loss [1]. Exposure to ototoxic medications (diuretics, salicylates, aminoglycosides, chemotherapeutics, etc.) can lead to sensorineural hearing loss, which may be temporary and reversible if identified early. Autoimmune hearing loss is characterized by a rapidly progressive or fluctuating bilateral sensorineural hearing loss with poor speech discrimination as well as vertigo and disequilibrium [1, 2]. Infections such as meningitis or labyrinthitis may also lead to hearing loss [1]. Sudden hearing loss occurring within 72 h window and unilateral hearing loss are additional categories of hearing loss that may occur due to a variety of reasons which include but are not limited to fracture to the temporal bone or other trauma to the inner ear, acoustic neuromas, or other cerebellopontine angle tumors, autoimmune, infectious, or may be considered idiopathic [2, 4].

Evaluation and Diagnosis

Hearing loss may simply be identified by asking, "Do you have trouble hearing?" Other hearing loss questionnaires exist, such as the "Hearing Handicap Inventory for the Elderly – Screening Version." Positive answers should further be questioned as to duration of hearing loss, if it has been sudden or gradual hearing loss, and whether it is unilateral or bilateral. It is important to ask occupational history as well as history of noise exposure. Further information may be elicited regarding family history of hearing loss, chronic medical problems, medication use, and any associated tinnitus, dizziness, or other ear problems [4].

The physical exam should consist of examining the auricle and periauricular tissues. An otoscope may be used to evaluate the external auditory canal for any cerumen or foreign objects. The tympanic membrane should be evaluated for surface anatomy, color, and mobility. The pneumatic bulb will aid in evaluating the tympanic membrane movement and aeration of the middle ear. Tuning fork tests can help differentiate between conductive and sensorineural hearing loss [1, 4]. Finally, evaluate the head, neck, and cranial nerves if clinically indicated [1].

Objective evaluation of hearing is commonly performed by pure tone audiometry. This is a diagnostic test that gives information on hearing loss to include the type and degree of hearing loss at a specific frequency threshold [1, 4]. A speech discrimination test can assess a patient's ability to understand speech and identify good candidates for hearing amplification with hearing aids [4]. Tympanometry is another simple test performed in the office, which evaluates the mobility of the tympanic membrane and function of the middle ear and Eustachian tube. Imaging may be indicated to further evaluate certain cases such as those with asymmetric or sudden hearing loss [1].

Treatment

A three-tiered approach is recommended for treatment of hearing loss: adult – assessment, education/counseling, and technology [4]. If a concern of hearing loss is identified and proper equipment is not available in the primary care office for appropriate evaluation, further assessment by audiology and/or otolaryngology is indicated [1, 5]. Counsel on and eliminate environmental noise and ototoxic agents if possible. Technological intervention is important, not only for hearing improvement but also for social and emotional function as well as for communication and cognition [3, 5].

In some cases, the only treatment option is hearing amplification. Hearing aids have several models to include those which fit behind the ear or in the canal. Assisted listening devices may be used for those unable to utilize hearing aids. Recent legislation in the United States has required the FDA to create a new class of over-the-counter hearing devices, which should increase access and decrease costs for hearing-impaired patients in the near future [2, 4]. Cochlear implant surgery is an option for those with severe

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sensorineural hearing loss [1, 4, 5]. Many etiologies of conductive hearing loss may also be corrected with surgery [1].

Referral to rehabilitation services may help teach patients to use nonverbal clues and vocational modification to ensure safe functioning despite his or her hearing impairment [1, 4].

Prevention

Prevention of some types of hearing loss may be impossible; however, prevention of exposure to ototoxic agents is possible by carefully choosing medications and discontinuing offending agents. Additionally, noise-induced sensorineural hearing loss may be prevented by screening for noise exposure, counseling about proper hearing protection, and avoidance of overexposure [1, 4].

Pediatric Hearing Loss

General Principles

Pediatric hearing loss is one of the most common sensory birth condition abnormalities in the United States affecting 1 to 3 per 1000 newborns [6–8]. Early detection of hearing loss before the age of 6 months is essential to prevent delays in language and other developmental milestones [7]. Although children with hearing loss often have complex needs, the consequences are treatable if hearing loss is detected and treated early in life [6].

Pathophysiology

Hearing loss in the neonate or child can be classified as congenital, acquired, or idiopathic. Of the congenital etiologies, it can be further classified as either syndromic or non-syndromic (non-syndromic can be autosomal recessive, autosomal dominant, or X-linked). Of the acquired cases of hearing loss, the great majority is considered environmental. Environmental risk factors to the neonate include cytomegalovirus, rubella, measles, syphilis, and exposure to alcohol. Other risk factors for neonates and children may include exposure to ototoxic drugs such as aminoglycosides or antineoplastic agents, hypoxic ischemic injury, or hyperbilirubinemia [7, 8].

Hearing loss may also develop later in childhood. Additional risk factors of childhood hearing loss include family history of childhood hearing loss, history of admission to the neonatal intensive care unit for greater than 5 days, history of mechanical ventilation/oxygenation requirement, craniofacial anomalies, infections associated with late onset hearing loss, head trauma, chemotherapy, recurrent otitis media, and caregiver concern [6, 7].

Hearing loss can be defined by degree, configuration, and type of loss. There are two major types of Hearing loss: adult – conductive hearing loss and sensorineural hearing loss. Conductive hearing loss is caused by problems with the outer or middle hear, whereas sensorineural hearing loss is caused by problems with the inner ear, auditory nerve, or central auditory pathway. Some children have mixed conductive and sensorineural hearing loss [2, 3].

Evaluation and Diagnosis

Newborn hearing screening is mandated in nearly every state in the United States. There are two main screening methods in the United States: the otoacoustic emission (OAE) test and the automated auditory brainstem response (AABR) test. The OAE allows for individual ear testing at any age and assesses for middle ear pathology. The AABR test evaluates the function of the auditory pathway to include the auditory nerve. The AABR is also often used as a follow up test if the OAE is failed during the initial newborn hearing exam. The Joint Committee on Infant Hearing (JCIH) recommends that infants who are admitted to the neonatal intensive care unit (NICU) for greater than 5 days be screened with the AABR [7].

If an infant does not pass initial screening tests, additional evaluation and referral should be completed before 3 months of age with intervention by 6 months of age. Other diagnostic tests exist but are primarily completed by an audiologist. These tests include diagnostic auditory brainstem response, tympanometry, diagnostic otoacoustic emissions, and behavioral hearing assessment [7].

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The physical exam should consist of particular attention to head size and symmetry, jaw size and symmetry, facial movement and symmetry, as well as external and middle ear morphology. Signs of the head and neck exam which may be related to hearing loss include malformation of the auricle or ear canal, dimpling or skin tags around the auricle, cleft lip or cleft palate, asymmetric facial structures, microcephaly, or tympanic membrane abnormalities. Many times, the physical exam will be normal. CT, MRI, and lab tests may further be ordered if clinically indicated [9].

Treatment

Any abnormal hearing test requires intervention. Appropriate referrals include those to otolaryngology, audiology, speech and language pathology, and a genetics specialist. Referrals to early intervention programs are essential. Early intervention services should be provided by professionals with expertise in hearing loss, speech and language pathology, and audiology. An ophthalmologic evaluation may also be appropriate if syndromic associations are identified [7].

Hearing aids are devices that amplify sound and transmit to the ear with the desired frequencies depending on the patient's diminished areas. These benefit patients with sensorineural hearing loss and some with conductive hearing loss. Assistive listening devices can be used in public places to help override poor acoustics [7].

Surgical implants are also an option in care for patients with severe hearing loss: adult – bone-anchored hearing aids are beneficial in children older than 5 who suffer from permanent conductive hearing loss. Cochlear implants amplify sound for children that are at least 1 year old and have profound bilateral sensorineural hearing loss [7].

Tinnitus

General Principles

Tinnitus is the perception of continuous or intermittent sound within the ears or head without an objective external stimulus. The noise has been described as ringing, buzzing, clicking, pulsations, roaring, hissing, sizzling, music, or voices. Although much of what we understand about tinnitus remains an enigma, it is considered a symptom, not a disease in and of itself. Tinnitus is often associated with sensorineural hearing loss, making inner ear or auditory tract dysfunction a viable source of tinnitus; however, the precise mechanisms and possible sites of involvement remain unclear [10]. Even when tinnitus is not severe, the perception can be extremely bothersome and often interferes with the daily activities of symptomatic individuals [10–12].

Pathophysiology

While there is no clear etiology of tinnitus, investigators suspect possible lesions or cochlear alterations within the limbic and nervous systems as the source of irregular neuronal activity in the lower auditory pathway. It is theorized that this stimulation of the auditory tract is the perceived sensations we collectively characterized as tinnitus [13]. There are some known risk factors for tinnitus [11, 13]:

- Exposure to high levels of recreational and occupational noise
- Ototoxic drugs: salicylates, quinine, aminoglycosides, antibiotics, antineoplastic agents
- Otologic diseases: otosclerosis, Meniere's disease, vestibular schwannoma (acoustic neuroma)
- Obesity
- Alcohol use
- Smoking
- Arthritis
- Hypertension
- Anxiety
- Depression
- Dysfunction of the temporal mandibular joint
- Hyperacusis

Tinnitus is most notable in patients who have been exposed to hazardous levels of industrial, recreational, or military-related noise [11]. Other underlying associations to tinnitus include nerve

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damage from brain trauma or lesions, inner ear damage, acute ear infections, foreign objects in the ear, allergies, ototoxic medications (aminoglycosides, aspirin, chemotherapeutics), stress, or low serotonin activity [11, 13].

Tinnitus can be characterized in several different ways, but most commonly, it is characterized as either "objective" or "subjective" tinnitus. Objective tinnitus can be heard by the examiner, usually with a stethoscope, and it is generally referred to as "pulsatile" tinnitus. If it synchronized with the heartbeat, it may be considered vascular in origin. If it is not, it may be originating from the middle ear or palatal muscles. Subjective tinnitus, on the other hand, is only heard by the patient. The tinnitus may be chronic or intermittent. It may be heard in one ear, both ears, or centrally within the head. The onset may be abrupt or insidious, and the severity may change with time as well [12, 13].

Evaluation and Diagnosis

The severity and sensation of tinnitus significantly vary among affected individuals. There is no current standardized guideline for the evaluation of tinnitus. Although serious pathology leading to tinnitus is rare, it is important to get a complete medical history to understand of any possible underlying causes [11, 12]. Assess the character of the tinnitus: (1) subjective versus objective, (2) location and quality, and (3) distinguished chronicity (chronic is considered at least 6 months duration). Subjective idiopathic tinnitus is the most commonly diagnosed type of tinnitus. There are several questionnaires to evaluate tinnitus to include the "Tinnitus Handicap Inventory" (THI) and the "Tinnitus Functional Index" [11]. Evaluate for any associated hearing loss and tympanic membrane dysfunction [12].

If asymmetric tinnitus is associated with asymmetric hearing loss or any other neurological deficits, further investigation and imaging is indicated. Likewise, for any heartbeat-synchronous pulsatile tinnitus, further evaluation with advanced imaging is indicated: this may include but is not limited to CT, MRI, CT angiography, MRI angiography, or ultrasound. If the tinnitus is unilateral and pulsatile or the tinnitus is associated with vertigo, it is recommended that the patient be referred to a specialty clinician [11].

Treatment

There have been multiple medications, to include complementary and alternative, studied to evaluate treatment of tinnitus, but none so far have demonstrated statistically significant improvements [11, 12]. There have been medical interventions studied such as transcranial magnetic stimulation, electromagnetic stimulation, low-level laser therapy, and acupuncture; however, none of these has shown consistent improvement of tinnitus either [11].

Sound therapy or sound maskers, which produce sound to cover the tinnitus, have not shown statistically significant improvement. Sound technologies, such as hearing aids (if the patient has associated hearing loss), may help mask tinnitus by increasing the overall level of ambient sound delivered to the patient. Cochlear implants may also help to mask tinnitus and improve perception of external noise; however, these are only for patients with profound sensorineural hearing loss [11].

Much of the treatment involved for treating tinnitus is truly aimed at treating the comorbid conditions associated with tinnitus such as anxiety, depression, hearing loss, and sleep disorders. Psychological and behavioral interventions are recommended to improve associated distress [11, 12].

Mindfulness-based cognitive therapy (MBCT) uses mediation techniques to address the burdens of tinnitus [14]. The goal of MBCT is to reframe an individual's outlook on the unpleasant experience of living with a chronic condition. This technical approach focuses on helping individuals adapt to distressing experiences by validating their personal thoughts, emotions, and sensations. Once acceptance is achieved, theorists believe the patient can focus on improving adaptive behaviors to combat the distressing experience such as tinnitus [14].

A recent study by Takahashi et al. expands on reports investigating the impact of psychological

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background on patients with tinnitus. Investigators argue that in order to improve the treatment of tinnitus, grading systems and protocols should take into consideration both psychological state and severity of tinnitus perception by affected individuals. Currently, THI does not incorporate the psychological background of patients with tinnitus into its severity grading system. Limited reports have found depression to be a significant factor on how the severity and sensation of tinnitus was perceived. Studies have found that patients with moderate to severe tinnitus have better therapeutic response to interventions when their psychiatric conditions were treated concurrently. This discovery has led some healthcare professionals to advocate for developing new protocols and parameters that utilize the Hospital Anxiety and Depression Scale (HADS) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)'s criteria for major depression and catastrophic events in addition to the THI when grading tinnitus severity and assessing for therapeutic intervention [10].

Unfortunately, there is no single effective treatment regimen to cure or significantly alleviate tinnitus. It is important to treat or eliminate comorbid conditions. Any surgical otologic disorders should be evaluated by otolaryngology [11].

Prevention

Because there is no effective treatment for most cases of tinnitus, the focus should be on prevention of known causes: reduce exposure to ototoxic drugs as well as avoid occupational and recreational loud noises [12].

Salivary Gland Inflammation and Salivary Stones

General Principles

Saliva plays an important role in the oral and digestive health. Composed of enzymes, electrolytes, and other molecules, saliva is an enrichened fluid that provides lubrication for the function of swallowing as well as aids in the digestion of starches through with salivary amylase [15]. Saliva also acts as a layer of protection against dental caries and oral pathogens. Major salivary glands include the parotid, submandibular, and sublingual glands. Additionally, there are minor salivary glands lining the oral cavity, pharynx, lips, and tongue [15]. Inflammatory conditions of the glands, also known as sialadenitis, are most common in the major salivary glands, with obstructive sialadenitis accounting for approximately one-half of benign salivary disorders treated in a primary care setting [15]. Other causes of inflammation of the salivary glands include infections (viral and bacterial), autoimmune disorders, and neoplasm of the salivary gland. While neoplasm of the salivary glands is relatively rare, they make up about 6% of all head and neck tumors [15]. Inflammation may be acute or chronic and can lead to salivary stone formation which will further enhance the inflammation in some cases [16].

Pathophysiology

Salivary gland stones, also known as sialoliths, develop when calcified mass forms within the salivary duct or gland [17]. The accumulation of salivary calculi can lead to mechanical obstruction within the duct, thus predisposing the gland to inflammation. The precise mechanisms leading to the developing of salivary stone are unclear. The "retrograde theory" of sialolith development postulates the migration of bacteria or food debris into the salivary gland ducts which later serves as a nidus for stone formation [17]. Another popular theory suggests that a localized inflammatory process causing the calcification of a mucus plug leads to the formation of sialoliths [18]. Other potential risk factors include use of tobacco products such as cigarettes. Very few studies have shown significant correlation between poor hygiene and salivary gland inflammation and stone development [17].

Acute bacterial sialadenitis is most often seen in the parotid gland in medically debilitated patients. Debilitation and dehydration may lead

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to the stasis of salivary flow which can generate stone precipitation and strictures of the salivary ducts. This environment favors bacterial infection, most commonly from *Staphylococcus aureus*, streptococcal species, and *Haemophilus influenzae* [15, 16]. Other infectious etiologies include *Mycobacterium*, *Toxoplasma*, and *Actinomyces* species [16].

Acute viral sialadenitis is most commonly found in the setting of mumps in children aged 4 through 6. Other viral causes include *Cytomegalovirus*, lymphocytic choriomeningitis virus, Coxsackie virus A, echo virus, and parainfluenza virus type C [16]. Predisposing factors for non-infectious acute sialadenitis include autoimmune disorders such as Sjogren's syndrome as well as chronic metabolic conditions such as diabetes mellitus and hypothyroidism [15].

Chronic sialadenitis is characterized by repeated episodes of pain and edema. Affected patients will often complain of intermittent pain and swelling of the gland, which is exacerbated during prandial salivary stimulation [14]. Furthermore, commonly prescribed medications such as diuretics, antihypertensive, antihistamines, antipsychotics, and antidepressants are known to decrease the salivary flow rate, which may play a limited role in facilitating stone formation and sialolithiasis [18, 19].

Neoplasms may be benign or malignant. Malignancies of the salivary gland are rare, encompassing only 16% of all salivary gland neoplasm cases [15].

Evaluation and Diagnosis

Acute bacterial sialadenitis has characteristic clinical findings of salivary gland pain and edema. Mucopurulent material can sometimes be expressed at the orifice of the nearby salivary duct [15, 16]. Acute viral sialadenitis is most commonly due to mumps offending the parotid gland, which is characterized by parotid edema with symptoms of fever, malaise, myalgias, and headaches in the weeks preceding the incubation period. Some children can experience recurrent viral sialadenitis. This can last weeks and recur every few months. Viral serology may help to confirm the diagnosis.

Chronic sialadenitis has characteristic findings of repeated episodes of pain and edema of the salivary glands. Generally, this occurs from little to no salivary flow and due to stones, strictures, or stenosis. It is sometimes possible to palpate the stone along the nearby duct [15].

Neoplasms typically present as painless, asymptomatic, slow-growing masses. Malignant neoplasms may present with findings such as facial paresis, fixation of the mass, and lymphadenopathy. Specialty referral to an otolaryngologist for further evaluation and possible biopsy is essential for an accurate diagnosis. A CT scan with contrast or MR with MR sialography may also be used to identify the mass's characteristics [15].

CT is the preferred modality for acute sialadenitis due to its sensitivity to calcification and spatial resolution. Extensive dental artifacts on CT imaging are a common limitation of this modality [19]. Ultrasound and MRI are also options; the clinical scenario will ultimately dictate the appropriate diagnostic imaging necessary for further evaluation. When imaging is inconclusive, further referral for US-guided fine needle aspiration and cytology may be indicated [19].

Treatment

Acute bacterial sialadenitis is treated by empiric antimicrobial therapy (i.e., Augmentin, etc.). Increasing salivary volume and flow by increasing hydration and utilizing sialagogues is also recommended. Salivary gland massage may also be useful.

Recurrent parotitis of childhood and chronic sialadenitis in adults are treated similarly as in acute cases as outlined above. It generally resolves spontaneously over time. Anti-inflammatory medications may also be considered.

Viral parotitis or mump treatment is primarily supportive and focuses on hydration and pain control. Mumps usually resolves spontaneously within weeks. Any stones contributing to acute

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or chronic sialadenitis may need surgical removal if conservative management fails [15].

Prevention

Vaccination has reduced the incidence of mumps by 99%. It is important to promote hydration and use sialagogues for enhancement of saliva production and prevention of stone formation [16].

Xerostomia

General Principles

Xerostomia is the subjective sensation of dry mouth. Its prevalence increases with age and tends to be higher in women than in men [20]. Major and minor salivary glands produce the saliva, which is composed of electrolytes, organic compounds, and water. Normal salivary function is to aid in digestion through oral processing and swallowing of food. Saliva protects the oral cavity by cleansing it, sustaining a neutral pH, preventing tooth demineralization, and adding an antimicrobial effect [21].

Pathophysiology

Xerostomia can occur with the reduction in the quantity, flow rate, or composition of the saliva produced. Hyposalivation is a pathological condition in which there is insufficient or decreased production of saliva [21]. Some cases of xerostomia may correlate with hyposalivation while others do not. Symptoms of xerostomia may range from oral discomfort to significant oral disease such as dental caries, periodontitis, dental erosion, and intraoral candidiasis that can negatively impact a patient's health, dietary habits, and quality of life [20, 21].

There are several causes of xerostomia such as dehydration, poor nutritional status, head or neck radiation, chemotherapy, salivary gland aplasia, Sjogren's syndrome, depression, smoking, and a variety of medications [21]:

- Antihypertensives
- Anticholinergics
- Antidepressants
- Antipsychotics
- Anxiolytics
- Diuretics
- Muscle relaxants
- Diuretics
- Muscle relaxants
- Sedatives
- Antiepileptics
- Antiparkinsonisms
- Antihistamines
- Cytotoxics
- Analgesics

Evaluation and Diagnosis

As with all ailments, a thorough medical history and exam are the chief means of attaining a diagnosis. It is important to identify any diseases that may put the patient at risk for the development of xerostomia or if the patient is on a medication regimen that may be inducing xerostomia, which is more common [20]. Patients may complain of dry mouth or other symptoms from dry mouth like a burning sensation or difficulty with speech and swallowing. He or she may also note a change in taste. On exam, the mucosal surfaces may be dry and the tongue swollen and dry, erythematous and atrophic oral mucosa, angular cheilitis or peeling lips [21].

Treatment

Treatment is aimed at identifying the underlying cause. Underlying systemic medical conditions such as Sjogren's disease, lymphoma, sarcoidosis, or amyloidosis may lead to xerostomia; treatment of these conditions may help the symptoms of dry mouth. If a medication is identified as causation, then it should be changed or eliminated if possible. It is important to encourage hydration, especially in the elderly and those with poor nutrition. Avoidance of food and drinks such as alcohol, sugar, and caffeine, which may lead to dry mouth or dental caries, is an essential dietary

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modification. Furthermore, if the patient is a current tobacco user, tobacco cessation should be encouraged [21].

There are a number of over-the-counter treatments available – toothpastes, rinses, lozenges, sprays, gels, oral patches, and chewing gums. Research suggests that when used in conjunction with prescription medication, the benefits can be additive, but when used alone, their efficacy is undetermined.

Two systemic medications available in the United States which may help stimulate saliva production (sialagogues): pilocarpine or cevimeline drops [21].

Hoarseness

General Principles

Hoarseness (or dysphonia) is a term used to describe a symptom or sign of altered voice quality [22]. The change in voice may be an alteration in quality, pitch, and loudness or may be described as breathy, strained, rough, or raspy [22, 23]. It is a common problem in the United States adult population affecting up to one-third of all adults at some point in time and leads to 2.5 million dollars in lost work cost [22].

Pathophysiology

The larynx houses the vocal folds, which are responsible for the production of sound as airflows pass these structures. The larynx extends from the base of the tongue to the trachea and is innervated by the superior and recurrent laryngeal nerves. There is a multitude of etiologies which may cause hoarseness. In general, these etiologies may be from irritants, inflammation, neuromuscular, psychiatric, systemic, or neoplastic disorders [23]. Table 1 outlines details of each of these categories.

Table 1 Etiologies of hoarseness (or dysphonia) in the adult population [23]

Irritants and inflammation	Acute laryngitis: viral, vocal abuse, allergies Chronic laryngitis: smoking, voice abuse, laryngopharyngeal reflux, allergies, inhaled corticosteroids
Neuromuscular	Vocal cord paralysis: Injury to recurrent laryngeal nerve, head and neck surgery (especially thyroid surgery), endotracheal intubation, mediastinal or apical immersion of lung cancer Muscle tension dystonia Spasmodic dysphonia (laryngeal dystonia)
Psychiatric	Stress and other psychiatric disorders
Systemic	Parkinson's disease Myasthenia gravis Multiple sclerosis Hypothyroidism Acromegaly Inflammatory arthritis
Neoplasms	Laryngeal papillomatosis Laryngeal leukoplakia Dysplasia or squamous cell carcinoma (risk factors: Smoking, alcohol use, chronic reflux)

Evaluation and Diagnosis

A careful history and physical exam are important to understand the etiology of the patient's hoarseness. Evaluate the onset and duration of voice changes. In the medical history, it is prudent to ask about any recent upper respiratory infections, allergies, or chronic medical problems. Assess for any associated symptoms of gastroesophageal reflux. In the social history, it is important to discuss any environmental exposures, tobacco use, or alcohol use. In addition, vocations in singing, teaching, and of the clergy are more at risk for this condition. Learning of any recent surgeries is also key. Associated symptoms such as cough, dysphagia, and odynophagia are important and may lead to more serious underlying causes of hoarseness [22, 23].

During the physical exam, it is important to assess for rhinorrhea, sneezing, or watery eyes which may suggest a more benign cause such as allergies or viral irritation; however, findings such as lymphadenopathy, stridor, and weight loss may be more concerning for serious etiologies such as malignancies. Stridor may indicate airway obstruction due to mass [23].

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Laryngoscopy may be performed at any point in time. Different recommendations exist as to when direct visualization is required. More recent guidelines suggest direct visualization is indicated if hoarseness persists for greater than 4 weeks [22]. The procedure should be done in the primary care office or referred to a specialist who has this capability. Direct visualization of the larynx should be done sooner if there is any suspicion of serious underlying condition. In case of tobacco or alcohol use, a neck mass, hemoptysis, dysphagia, odynophagia, neurological symptoms, unexplained weight loss, aspiration of a foreign body, and persistent symptoms after surgery or if the hoarseness significantly impairs the quality of life of the patient, then visualization is more urgent [22, 23].

Imaging, such as a CT or MRI, may be used to assess specific pathology; however, it is recommended that direct visualization be performed prior to any imaging [22].

In cases of pediatric hoarseness, it is generally indicated for the patient to be referred to otolaryngology and speech and language pathology early [24].

Treatment

If hoarseness duration is less than 2 weeks (acute), it is more likely to be benign. Reassurance is appropriate but also address and treat any underlying etiologies such as viral infections, allergies, and reflux. If reflux is suspected through history or visualization of chronic laryngitis, then a trial of a high-dose proton pump inhibitor (PPI) is warranted; however, isolated dysphonia should not be treated with PPI therapy without visualization first. Likewise, antibiotics are usually not indicated in treating hoarseness [22, 23]. If corticosteroids are on the patient's medication list, the clinician may recommend a decrease or alteration in the dose or type of corticosteroid used for 4 weeks. Inhaled fluticasone (Flovent) is the most common offending agent [23]. Oral corticosteroids to treat hoarseness are not recommended without visualization of the larynx [22]. If there is a systemic condition which has a known symptom of hoarseness (such as hypothyroidism), optimize treatment for the condition, and reassess after 4 weeks.

If laryngoscopy is completed and no serious pathology is found, it is recommended the patient be referred for vocal hygiene training and voice therapy by a speech and language pathologist.

Surgery may be indicated for any findings of benign or malignant masses, glottic insufficiency, or if airway obstruction is a risk [22, 23].

Prevention

Educate of the patient on measures to reduce voice disorders: adequately hydrate with water, use amplification devices to reduce voice strain, rest the voice briefly, and provide indoor air humidification. Additionally, educate the patient on avoidance of triggers such as tobacco smoke, certain medications, environmental irritants or allergens, and vocational abuse of the voice [22, 23].

Epistaxis

General Principles

Epistaxis is a common condition that can affect up to 60% of the general population [25]. Up to 9% of the pediatric population experiences recurrent epistaxis. Epistaxis is generally categorized as anterior (90%) or posterior (10% of cases but more severe). Epistaxis has a bimodal distribution 2–10 and 50–80 years of age [25, 26]. Anterior epistaxis generates from either Kiesselbach's plexus or the anterior inferior turbinate [26]. Posterior epistaxis results from bleeding of the posterior edge of the nasal septum or the posterior lateral nasal wall mucosa [29].

Pathophysiology

The etiology of epistaxis can be divided into two general causes: local and systemic. Local causes refer to specific complications to the nasal mucosa. Systemic causes refer to more systemic

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etiologies causing epistaxis to be more likely [25, 29]. See Table 2 for a list of local and systemic causes of epistaxis.

In children, the most common etiology of anterior epistaxis is trauma (usually nose picking) [29]. Idiopathic nose bleeding occurring at night is also common in children but is eventually outgrown. Posterior epistaxis in children is most often due to juvenile nasopharyngeal angiofibroma, which is most commonly seen in teenage boys. Similar to adults, systemic disease of childhood may also lead to epistaxis such as (1) vascular anomalies: hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome); (2) hematologic problems (genetic or acquired) such as primary idiopathic thrombocytopenic purpura, leukemia, or aspirin use; or (3) coagulopathies (genetic or acquired) such as von Willebrand disease, hemophilia, warfarin use, liver diseases leading to coagulopathy, or drug-related thrombocytopenic purpura [28].

Evaluation and Diagnosis

Anterior epistaxis is generally obvious to the examiner, and blood loss is usually not significant.

Table 2 Local and systemic causes of epistaxis [25, 29]

Local causes	Systemic causes
Trauma	Hypertension
Nose picking	Antiplatelet medications
Foreign objects stuck in nose	Hereditary hemorrhagic telangiectasia
Neoplasms or polyps (nasopharyngeal angiofibroma)	Hemophilia
Rhinitis or sinusitis (chronic, acute, allergic)	Leukemia
Medications (inhaled corticosteroids)	Liver disease
Irritants (occupational exposures, cigarettes, etc.)	Medications (aspirin, anticoagulants, NSAIDS)
Septal perforation	Platelet dysfunction
Vascular malformations or telangiectasia	Thrombocytopenia
Environmental: Dry and low humidity	

Posterior epistaxis may be associated with a large volume of blood loss but may present insidiously with symptoms such as nausea, hematemesis, hemoptysis, or melena [25, 27]. It is important to identify the likely source of bleeding (anterior or posterior) as well as inquire about the history leading up to the epistaxis episode in order to understand if further workup is necessary. Estimate the volume of blood loss, time of onset, frequency of any prior episodes, any medical comorbidities, acute respiratory infections, use of medications, recreational drug use, and any recent surgery or trauma. In more severe cases, airway protection and hemodynamic stability must be considered. Any concern of clinical instability should be managed in the emergency department [26, 27, 29].

In stable scenarios, the physical exam may be performed with the aid of a vasoconstrictor spray or gauze soaked in a vasoconstrictor. Physical exam ideally should be done with nasal speculum and light source. This in combination with an anesthetic may be helpful during the physical exam to successfully identify the source of bleeding [25, 26].

Treatment

Because 90% of epistaxis cases are anterior, most cases of epistaxis are treated successfully with conservative therapies [26]. Initial treatment consists of pinching the lower portion of the nose against the anterior nasal septum placing pressure along the ala for several minutes. Cotton-tipped applicators or cotton balls can be used to place pressure against the source of bleeding. These items may be soaked in topical vasoconstrictors or decongestants if needed [25–27]. It is important to tilt the head forward, not backward, in order to avoid pooling of the blood, which can lead to airway obstruction [26]. If direct pressure is not helpful, silver nitrate sticks or electrocautery may be applied to the area of bleeding. Apply the cauterization instrument directly to the source of bleeding to avoid any excessive soft tissue damage; do not cauterize blindly [25, 27]. Avoid cauterizing bilaterally due to risk of septal necrosis

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and perforation. If bilateral cauterization is needed, it is optimal to perform cauterization 4–6 weeks apart [26, 27].

If this initial management is unsuccessful, nasal packing may be an effective next step. There is data showing that using tranexamic acid (TXA) soaked pledgets before nasal packing may stop bleeding within 10 min of application in up to 71% of subjects [27]. There are many commercial products or commercial nasal tampons available for nasal packing. The principle is to localize the source and apply packing to stop the site of bleeding. The packing may be left in for several days [26, 27]. If anterior packing is unsuccessful, then one can move to posterior packing, which is a more complex procedure. If this is necessary, specialty consultation and admission to the hospital are recommended due to complexity and risks involved in the procedure. Toxic shock syndrome is a risk in the setting of any type of packing techniques. Anti-staphylococcal antibiotic (oral or topical) may be considered as prophylactic therapy, with special attention for patients who are immunocompromised, have heart valve disease or receiving posterior nasal packing [27]. Similar to posterior packing for persistent anterior bleeding, posterior bleeding should be treated in the hospital setting and with specialty consultation. Additional intervention may be indicated such as arterial embolization or arterial ligation [25–27].

In summary, epistaxis, in particular anterior epistaxis, is a common condition that can be treated in the outpatient setting with conservative measures; however, in cases of persistent bleeding or posterior epistaxis, more invasive measures performed with specialty consultation in the hospital may be necessary.

Prevention

If recurrent anterior epistaxis persists, consider underlying etiologies. If underlying pathology is ruled out, various treatments may be helpful in prevention such as humidification of air, application of petroleum jelly to the local area to maintain humidity, or application of antiseptic creams. Abstain from alcohol and avoid hot drinks that cause vasodilation [27, 29].

Foreign Bodies in the Ear and Nose

General Principles

Foreign bodies lodged in the ear and nose are a problem commonly seen in children and patients with mental handicaps. At times, it can be difficult to diagnose as the object placement may not have been observed by the parent or caregiver. Common foreign bodies found in the ear or nose include beads, rubber erasers, toy parts, pebbles, food, marbles, and button batteries [30–32].

Pathophysiology

Although a nasal foreign body can be found in any portion of the nasal cavity, it is most commonly found in one of two places: below the inferior turbinate and anterior to the middle turbinate.

A foreign body within the ear is usually lodged at the point where the external auditory canal narrows into a bony cartilaginous junction. If lodged too far, the tympanic membrane can be damaged [30, 32].

Evaluation and Diagnosis

A nasal cavity foreign body may be asymptomatic; however, it may also present as unilateral, malodorous, mucopurulent nasal discharge or intermittent epistaxis. Other complications include posterior dislodgement with risk of aspiration, trauma due to initial placement or self-removal attempts, and infection [31].

When evaluating a patient for a nasal foreign body, it is useful to apply a topical vasoconstriction agent to reduce mucosal edema, such as 0.5% phenylephrine or oxymetazoline [30, 32]. Anesthesia may also be accomplished with a topical spray such as 4% lidocaine. If no foreign body is visualized on physical exam, a plain film of the sinus or CT scan may be considered [30].

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A foreign object in the ear may also be asymptomatic or an incidental finding on exam. Symptoms can include otitis, hearing loss, or purulent drainage. It is important to appropriately visualize the object in order to decrease trauma. If it is not easily visualized or if there is evidence of a perforated tympanic membrane, it may be necessary to refer to a specialty physician. Topical anesthesia of the ear is generally not required for foreign body removal [30].

Treatment

In most cases, a foreign object in the nose or ear is not an emergency, so removal may be delayed if it is not easily achieved in the family physician's office. It is appropriate, then, to refer to an otolaryngologist. In the event a caustic object is present (batteries, etc.) irrigation should not be used, and a referral is urgent [30].

Removal of a nasal cavity foreign object may be completed by several different techniques. Most commonly, if the object is in the anterior passage, it may be graspable with a forceps, curved hooks, cerumen loops, or suction catheter [32]. A balloon tip catheter may be used by lubricating the balloon tip, passing the tip past the foreign body, inflating, and then pulling forward [31]. The "parental kiss" is a less invasive option in children in which the parent provides a puff of air through the child's mouth with the unaffected nostril occluded, providing positive pressure to expel the foreign body [30–32]. Once the object is removed, it is important to reinspect the nasal cavity for any additional objects or localized trauma. If the object is not successfully removed, it may be necessary to refer to an otolaryngologist.

Removal of a foreign object within the external auditory canal may be performed using similar techniques as mentioned above. Irrigation is another option, which may be helpful to flush out small objects closer to the tympanic membrane [30, 32]. If a live insect is present, it is important that it be killed prior to removal. Alcohol, 2% lidocaine, or mineral oil may be instilled in the canal [32]. This should be done only if the tympanic membrane is intact. If the object is not easily graspable, however, there are higher rates of complications such as canal lacerations and tympanic membrane damage. In the event of unsuccessful removal, high risk of trauma, or if there is need for anesthesia, specialty referral is recommended [30].

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Part XVII

The Cardiovascular System

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Hypertension

79

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General Principles

Hypertension, also referred to as high blood pressure (BP), is one of the most common conditions seen in adult primary care practices. In 2016, there were nearly 33 million visits to provider offices with essential hypertension as the principle diagnosis [1]. In 2017, age-adjusted prevalence data in the United States reveals that 46% of adults aged ≥20 years have hypertension, which equates to an estimated 116.4 million men and women [2]. Worldwide, at least 1.39 billion adults have high blood pressure [3].

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Hypertension remains a major risk factor for cardiovascular and cerebrovascular disease. From a population health perspective, the elimination of hypertension could reduce cardiovascular mortality by 30% in men and 38% in women, which translates to a larger impact on mortality for all risk factors among females and all but smoking cessation among males [4]. In addition to a reduction of mortality, management of uncontrolled hypertension substantially reduces the risk of heart failure, stroke, myocardial infarction, and chronic kidney disease.

As knowledge and analysis of population trends deepen, it has become apparent that certain populations bear a greater burden of illness from hypertension and its consequences both in the United States and globally. There is a widening disparity of prevalence and control among individuals from low- and middle-income countries compared to those from high-income countries [5]. In addition, regarding race/ethnicity, non-Hispanic blacks in the United States have higher age-adjusted prevalence and unmet treatment goals for hypertension than other racial groups. When compared to non-Hispanic white patients, there is a larger proportion of Mexican-Americans and people of other races/ethnicities not receiving treatment for hypertension despite the indication [5].

The diagnosis and management of hypertension has been complicated by the release of multiple guidelines in the last decade which are supported by varying degrees of evidence. In addition to age, race/ethnicity, and comorbid condition-specific management recommendations, these guidelines contain potentially conflicting recommendations for diagnostic and treatment thresholds. Thankfully, they are consistent regarding the first-line pharmacological treatments recommended which include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers. In addition, among all guidelines, recommendations are consistent regarding renewed emphasis on and reaffirmation of the importance of accurate diagnosis, lifestyle modifications, and individualized management approaches.

Overall, management of hypertension remains a challenge in primary care. Providers are tasked with accurately detecting high blood pressure, managing comorbidities, minimizing side effects, maintaining quality of life, and promoting healthy lifestyle choices, all with the goal of reducing cardiovascular risk.

Detection and Diagnosis

There is ample evidence to support the benefits of screening for high blood pressure in adults. In the landmark report made by the seventh Joint National Committee (JNC 7) in 2003, recommendations were made to screen adults every 2 years if blood pressure was recorded as less than 120/80 mm Hg and every 1 year for systolic blood pressures 120–139 mm Hg or diastolic pressures 80–90 mm Hg [6]. The report from the eighth Joint National Committee (JNC 8) did not address nor define the diagnosis of hypertension in its 2014 guideline [7]. Rather, the 2014 guideline focused on management principles based upon age (greater than or younger than 60) as well as comorbid conditions like diabetes and chronic kidney disease.

The American Academy of Family Physicians (AAFP) supports the US Preventive Services Task Force (USPSTF) clinical preventive service recommendations on this topic which suggests screening all adults over 18 for hypertension. The USPSTF recommends annual screening for adults aged 40 years or older and for those at increased risk for high blood pressure. Persons deemed at increased risk include those who have high-normal blood pressure (130 to 139/85 to 89 mm Hg), those who are overweight or obese, and African Americans. Adults aged 18–39 years with normal blood pressure (<130/85 mm Hg) who do not have other risk factors should be rescreened every 3–5 years. It is important to note that previous recommendation statements from the USPSTF did not differentiate blood pressure measurement protocols nor create a reference standard for measurement confirmation. The most current USPSTF recommendation, however, added to the yearly screening guidance by including language regarding method of measurement, specifically assessing the diagnostic accuracies of office blood pressure measurement,

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ambulatory blood pressure monitoring (ABPM), and home blood pressure monitoring (HBPM). The USPSTF concluded that obtaining measurements outside of the clinical setting is necessary for diagnostic confirmation before starting treatment [8].

Guidelines and typical practice patterns suggest that the diagnosis should be based on at least two separately recorded elevated blood pressure readings. In a patient with a single greatly elevated blood pressure reading in the office setting who already has hypertensive-related target organ damage, the diagnosis can generally be made without follow-up readings. Table 1 gives an overview of office-based blood pressure and hypertension classifications based on current guidelines. This table includes information from the 2018 European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) definition of high blood pressure, which is defined as office systolic blood pressure value of >140 mm Hg and/or diastolic blood pressure value of >90 mm Hg [9].

Traditionally, blood pressure is recorded in the office with an auscultatory or oscillometric method manually or via an automated device. Patients should be seated quietly for at least 5 min in a chair with feet on the floor and arm supported. Transient elevations in blood pressure can occur as a result of certain substances like nicotine, alcohol, cocaine, or caffeine in addition to commonly utilized medications like nonsteroidal anti-inflammatory medications, antidepressants, oral contraceptives, and decongestants [10]. Table 2 outlines some more of these common substances. As mentioned, the JNC 8 report does not address screening intervals, nor does the American College of Cardiology (ACC)/American Heart Association (AHA) guideline, which was released as an update to the JNC 7. It does, however, conclude that the diagnosis of hypertension should be based on accurate measurement and confirmation, which ultimately aligns with other US and international guidelines [9, 10, 11].

The USPSTF found convincing evidence that ABPM is the best method for diagnosing hypertension. However, ABPM is not widely available. The USPSTF found good quality evidence that HBPM may be an acceptable alternative [8]. Both ABPM and HBPM permit recognition of white coat hypertension (i.e., elevated blood pressure level that occurs only in clinical settings), thus helpful in confirmation of a hypertension diagnosis. HBPM also facilitates self-monitoring of blood pressure, which likely has benefits in awareness, adherence, and ultimately blood pressure reduction. Home blood pressure measurement technique is also important, and providers should instruct patients on proper monitoring protocols. The 2017 ACC/AHA guidelines provided a reference regarding the relationship between HBPM blood pressure readings, ABPM readings, and corresponding office-based measurements, which is summarized in Table 3 [10]. Note that the threshold for stage 1 and stage 2 hypertension based on these guidelines is achieved with lower HBPM and ABPM measurements.

Approach to the Patient

Cornerstones in the evaluation of patients with newly diagnosed hypertension include (1) assessing overall cardiovascular mortality

Table 1 Classification of blood pressure level for adults

Guideline (year released)	Normal blood pressure	Elevated blood pressure or prehypertension[a]	Stage 1 hypertension[b]	Stage 2 hypertension[b]
JNC 7 (2003)	<120/80	120–139/80–89	140–159/90–99	>160/100
JNC 8 (2014)	Not defined	Not defined	Not defined	Not defined
ACC/AHA (2017)	<120/80	120–129/80	130–139/80–89	>140/90
ESC/ESH (2018)	120–129/80–84	130–139/85–89	140–159/90–99	160–179/100–109

[a]Prehypertension category was removed from JNC 8 and AHA/ACC guidelines.
[b]ESC/ESH guidelines use "Grade" language instead of "Stage" and defines Grade 3 HTN as >180/110.

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Table 2 Drugs that may cause blood pressure (BP) elevation

Drug	Common examples
Estrogen	Oral contraceptives, hormone replacement therapy
Herbals	Ephedra, ginseng
Illicit drugs	Amphetamines, cocaine
Nonsteroidal anti-inflammatories	Ibuprofen, naproxen
Psychiatric agents	Fluoxetine, lithium, tricyclic agents (TCAs)
Steroids	Prednisone
Sympathomimetics	Over-the-counter nasal decongestants

Table 3 ACC/AHA corresponding values of SBP/DBP for clinic, HBPM, daytime, nighttime, and 24-h ABPM measurements

Office measurement	HBPM	Daytime ABPM	Nighttime ABPM	24-hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ABPM indicates ambulatory blood pressure monitoring, *BP* blood pressure, *DBP* diastolic blood pressure, *HBPM* home blood pressure monitoring, *SBP* systolic blood pressure.
Source: [10].

risk and presence of comorbid cardiovascular disease risk factors, (2) investigating for secondary causes of high blood pressure, and (3) determining if the patient has evidence of end-organ damage. A thorough history and physical examination with targeted laboratory and diagnostic studies will assist the clinician in a comprehensive evaluation toward these goals.

History

Hypertension is the result of a complex interaction between genetic predisposition and various environmental exposures including diet, physical activity, and medication/substance use. Physical inactivity, being overweight or obese, and excess intake of alcohol or nicotine contribute to a large proportion of underlying hypertension. Providers should inquire about a patient's history of previously elevated blood pressures and specific conditions like diabetes, hyperlipidemia, and obstructive sleep apnea as well as specific risk factors. Table 4 outlines some of the well-documented modifiable and fixed risk factors common in patients with high blood pressure. Given evidence of disparities of disease prevalence and burden previously mentioned, stress and even discrimination have been linked to hypertension [12], so providers should strongly consider asking patients and their families about social determinants of health that may influence decision-making, adherence, and overall wellness.

Table 4 Cardiovascular disease risk factors common in patients with hypertension

Age (>55 men or >65 women)
Chronic kidney disease
Cigarette smoking
Diabetes obesity (body mass index >30)
Dyslipidemia/hypercholesterolemia
Family history of hypertension
Family history of premature cardiovascular disease (first-degree male relative <55 years, female <65 years)
Microalbuminuria or GFR <60 mL/min
Obstructive sleep apnea
Overweight/obesity
Physical inactivity/low fitness level
Poor/unhealthy diet
Psychosocial stress

Physical Examination

Each patient newly diagnosed with hypertension should have a physical exam including more than one blood pressure measurement with adherence to proper technique. At least at the initial diagnosis, blood pressure should be measured in both arms in addition to assessments in both the standing and sitting positions. In subsequent visits, the arm with the higher reading should be used. The exam should also include (1) calculation of the body mass index (BMI), (2) evaluation of the optic fundi, (3) exam of the neck including palpation of the thyroid gland and auscultation for

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carotid bruits, (4) cardiac exam, (5) lung exam, (6) abdominal examination with special attention for enlarged kidneys, masses, abdominal aortic pulsation, and abdominal or renal bruits, (7) examination of the lower extremities for pulses and edema, and (7) a neurological evaluation.

Laboratory Tests and Diagnostic Procedures

Laboratory and diagnostic testing are valuable tools not only in determining the presence of end-organ damage at the time of diagnosis but also in identifying secondary causes of hypertension. In addition, baseline laboratory tests are also important in cardiovascular risk factor profiling which facilitates effective treatment planning. Recommended tests include serum potassium and sodium levels, blood urea nitrogen, and creatinine level. An electrocardiogram (ECG), blood glucose, hematocrit, and fasting lipid panel are also recommended, if not done previously, to help assess overall cardiovascular risk. The ECG also may reveal target organ damage in the form of left ventricular hypertrophy or prior myocardial infarction (Q waves). Optional tests include a TSH level and calcium. A decision to perform other tests such as a chest radiograph, uric acid level, or echocardiogram are appropriate if indicated based on findings from history, physical exam, or ECG or in instances of historical clues suggesting a secondary cause of hypertension.

Secondary Causes

Though most cases of hypertension are considered idiopathic or primary, it is important to consider secondary causes of hypertension at the time of diagnosis. Secondary causes of hypertension are identifiable and potentially reversible causes of elevated blood pressures. It is estimated that one of these specific and remediable causes is identified in approximately 10% of patients (9). The most common secondary causes are obstructive sleep apnea, renal artery stenosis, and hyperaldosteronism. Secondary hypertension should be suspected in younger patients (less than 30 years of age) as well as in patients with treatment-resistant high blood pressure. As noted in Table 2, there are multiple substances and medications that cause elevations in blood pressure. A trial off potentially offending medications (if possible), or a change in diet, may be warranted before embarking on pharmacologic treatment. Specialty colleague consultation is often necessary in the evaluation of secondary hypertension due to the complex measurements and data interpretation necessary to properly diagnose these conditions.

Management

Benefits of Treatment

In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35–40%; myocardial infarction, 20–25%; and heart failure, more than 50% [13]. These data support the importance of treating patients to not only reduce BP but to also, more importantly, prevent the morbidity and mortality associated with hypertension.

The panel members appointed to the eighth Joint National Committee (JNC 8) provided an evidence-based update to BP treatment goals. Per their report, in the general population aged $\geq$60 years, pharmacologic treatment should be initiated to lower BP at systolic BP $\geq$150 mm Hg or diastolic BP $\geq$90 mm Hg and treat to a goal systolic BP $<$150 mm Hg and goal diastolic BP $<$90 mm Hg. This recommendation is made with Grade A (i.e., highest level) evidence. For patients $<$60 years of age, expert opinion recommendation is to initiate treatment with a systolic BP of $\geq$140 mm Hg and treat to a goal of $<$140 mm Hg, and grade A recommendation is to initiate pharmacologic treatment to lower BP at diastolic BP $\geq$90 mm Hg and treat to a goal $<$90 mm Hg. In the population aged $\geq$18 years with chronic kidney disease (CKD) or diabetes, the recommendation is to initiate pharmacologic treatment at systolic BP $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg and treat to goal $<$140/90 mm Hg [7].

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The 2017 ACC/AHA guidelines recommend incorporating cardiovascular risk estimates with BP levels to determine when to initiate antihypertensives. The guidelines suggest initiating medication in those at high cardiovascular risk when systolic BP is 130 mm Hg or greater or diastolic BP is 80 mm Hg or greater. In those at lower risk, they suggest initiating antihypertensives when systolic BP is 140 mm Hg or greater or diastolic BP is 90 mm Hg or greater (10). High risk is defined as a history of clinical cardiovascular disease or an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher according to the pooled cohort equations. Clinical disease is defined as coronary artery disease, heart failure, or stroke [10]. A target close to 120/80 mmHg is generally better than a higher BP target.

Nonpharmacologic Interventions

All patients with blood pressures above normal should be treated with nonpharmacologic interventions: heart-healthy diet, reducing sodium intake, potassium supplementation, increasing physical activity, limiting alcohol consumption, and losing body weight for those who are overweight [10]. Table 5 is a summary of some key recommendations for lifestyle changes that lower blood pressure. For overall cardiovascular disease risk reduction, all patients who smoke should be counseled about smoking cessation and provided with assistance modalities.

The DASH eating plan emphasizes intake of vegetables, fruits, and whole grains. Additionally, low-fat dairy products, poultry, fish, legumes, and nuts should be included. Diet should be rich in calcium and potassium. Intake of sweets, sugar-sweetened beverages, and red meats should be limited. Sodium intake should be no more than 2400 mg each day. Research has shown that a DASH eating plan with no more than 1600-mg sodium has effects similar to single drug therapy [14].

Adults with elevated BP should be encouraged to engage in aerobic physical activity to lower BP. The recommendation is to include three to four sessions per week lasting an average of 40 min per session and involving moderate- to vigorous-intensity physical activity [15].

Some research has shown increased blood pressure to be positively correlated to more than 2 ounces/day of alcohol. Therefore, it is important to limit alcohol intake [16]. Alcohol should be limited to no more than one ounce (30 mL) of ethanol per day for women and no more than two ounces (60 mL) per day for men.

Pharmacologic Treatment

When deciding on pharmacologic therapy, the individual patient characteristics, including age, race, sex, family history, cardiovascular risk factors, and concomitant disease states, should be considered. Additionally, the patient's ability to afford the prescribed therapy as well as their compliance must be considered.

In the general population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. In the

Table 5 Lifestyle recommendations for hypertension

Recommendation	Description	Approximate systolic BP reduction
DASH eating plan	Diet rich in fruits, vegetables, and low-fat dairy with reduced fat intake	8–14 mm Hg
Exercise	Regular aerobic activity at least 30 min per day	4–9 mm Hg
Reduced dietary sodium intake	Maximum 2400 mg (ideally 1600 mg) of sodium daily	2–8 mm Hg
Moderate alcohol drinking	Maximum 2 ounces ethanol per day for men; maximum 1 ounce per day for women	2–4 mm Hg
Weight loss	Achieve/maintain BMI of 18.5–24.9 kg/m^2	5–20 mm Hg

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population aged ≥18 years with chronic kidney disease (CKD), initial (or add-on) antihypertensive treatment should include an ACE inhibitor or ARB to improve kidney outcomes. This recommendation applies to all CKD patients with hypertension regardless of race or diabetes status. Note that an ACE inhibitor and ARB should not be used together [17].

The main objective of hypertension treatment is to attain and maintain goal blood pressure. If goal BP is not reached within a month of treatment, the initial drug dose should be increased or a second drug such as a thiazide-type diuretic, CCB, ACE inhibitor, or ARB should be added. If the goal BP cannot be reached with two agents, a third drug should be added [7]. It has been suggested that a 6-month period of undertreated hypertension increases cardiovascular morbidity [18] (Fig. 1).

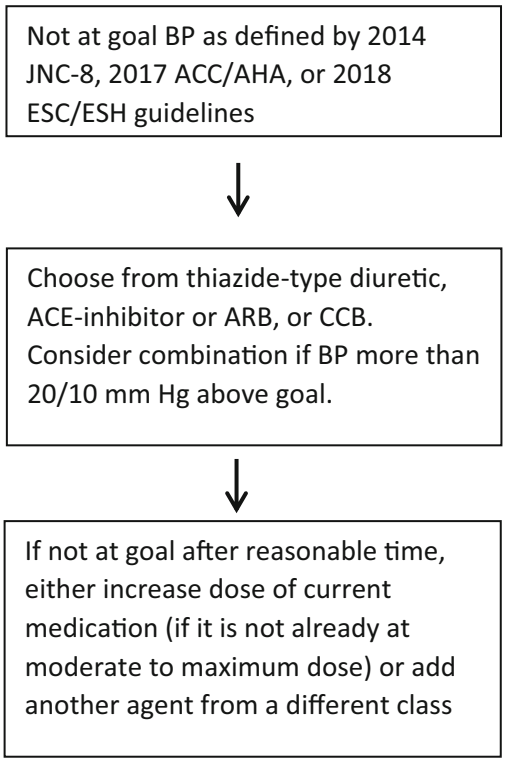


Fig. 1 Evidence-based simplified algorithm for hypertension treatment

Diuretics

Thiazide-type diuretics (chlorthalidone, hydrochlorothiazide) increase renal excretion of sodium and chloride at the distal segment of the renal tubule which results in decreased plasma volume, cardiac output, and renal blood flow and increased renin activity. With these agents, potassium excretion is increased, while calcium and uric acid elimination is decreased. Because of its greater potency and longer duration, chlorthalidone should be preferred over hydrochlorothiazide, especially when used alone. Potential side effects of all thiazide-type diuretics include hyponatremia, hypokalemia, dizziness, fatigue, muscle cramps, gout attacks, and impotence. Special attention should be paid when starting these agents in patients with diabetes, elevated cholesterol, or gout as thiazides can worsen each of these conditions. None of these conditions is a contraindication, however.

Loop diuretics and potassium-sparing diuretics can be used as adjunct therapy when thiazide-type diuretics are not sufficient (e.g., in patients with decreased glomerular filtration rate). Loop diuretics (furosemide, torsemide, and bumetanide) inhibit sodium and chloride reabsorption in the proximal and distal tubules and the loop of Henle. Side effects include diarrhea, headache, blurred vision, tinnitus, muscle cramps, fatigue, or weakness. When used in high doses in patients with significant renal disease, ototoxicity may occur.

Potassium-sparing diuretics (spironolactone, triamterene, amiloride) are useful for preventing potassium wastage that occurs with thiazide and loop diuretics. Spironolactone competitively inhibits the uptake of aldosterone at the receptor site in the distal tubule, in turn reducing the effect of aldosterone. This drug is an evidence-based fourth-line medication for resistant hypertension (described below). Main adverse effects to be aware of include gynecomastia and hyperkalemia. Triamterene and amiloride are typically used more specifically to stop potassium loss, and both have side effect profiles similar to the thiazide diuretics [19].

ACE Inhibitors

ACE inhibitors block the conversion of angiotensin I to angiotensin II, resulting in decreased aldosterone production with subsequent increased

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sodium and water excretion. As a result, renal blood flow is increased and peripheral resistance decreases. Renin and potassium levels typically increase. Major side effects include cough, angioedema, and the possibility of acute renal failure (in patients with renal artery stenosis). Importantly, this class of medication can cause syncope in patients who are salt, or volume, depleted. This drug class is teratogenic in the human fetus and should therefore be avoided in pregnancy and in women who may become pregnant.

ACE inhibitors have little effect on insulin and glucose levels or lipid levels, making them a good choice for most diabetics and patients with hyperlipidemia. ACE inhibitors are a particularly good choice for patients with congestive heart failure, peripheral vascular disease, and renal insufficiency as well.

Angiotensin Receptor Antagonists

ARBs bind to angiotensin II receptors, blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Aldosterone production decreases, while plasma renin and angiotensin II levels rise. There is no notable change in the serum potassium level, renal plasma flow, glomerular filtration rate, heart rate, cholesterol level, or serum glucose.

ARBs are generally well-tolerated but can cause hyperkalemia. ARBs are also teratogenic and should be avoided in patients of childbearing age. The major use of ARBs is for patients who cannot tolerate an ACE inhibitor due to cough.

Calcium Channel Blockers

CCBs reduce the influx of calcium across cell membranes in myocardial and smooth muscles. This in turn dilates coronary arteries, as well as peripheral arteries. This dilation reduces total peripheral resistance leading to decreased BP. Structural differences exist between agents in this class, which lead to different adverse effect profiles as well as differences in their effect on cardiac conduction. Verapamil and diltiazem (non-dihydropyridines) work to slow the conduction through the AV node and prolong the effective refractory period in the AV node. Dihydropyridines (e.g., amlodipine, nifedipine) increase cardiac output and have a more profound vasodilatory effect, making them the preferred CCBs for hypertension.

The main noteworthy side effect of dihydropyridine CCBs is peripheral edema, but they can also cause constipation, flushing, and tachycardia. CCBs are contraindicated in patients with heart block, acute myocardial infarction, and cardiogenic shock. CCBs have no effect on glucose metabolism or lipid levels. CCBs are a particularly good choice for patients with migraine headaches, angina, chronic obstructive pulmonary disease or asthma, peripheral vascular disease, renal insufficiency, supraventricular arrhythmias, and diabetes.

Beta-Blockers

Beta-blockers are not indicated for first-line treatment of uncomplicated hypertension but are recommended for patients following a myocardial infarction and for patients with congestive heart failure. Beta-blockers antagonize the effects of sympathetic nerve stimulation or circulating catecholamines at beta-adrenergic receptors, which are widely distributed throughout the body. Beta-1 receptors are predominant in the heart (and the kidney), while beta-2 receptors are predominant in other organs such as the lung, peripheral blood vessels, and skeletal muscle. In the kidney, the blockade of B1 receptors inhibits the release of renin from the juxtaglomerular cells and thereby reduces the activity of the renin-angiotensin-aldosterone system. In the heart, blockade of B1 receptors in the sinoatrial (SA) node reduces heart rate, and blockade of the B1 receptors in the myocardium decreases contractility. It is likely a combination of these effects that leads to BP reduction. The overall clinical response to beta-blockers is a decreased heart rate, decreased cardiac output, lower blood pressure, decreased renin production, and bronchiolar constriction.

The side effect profile of beta-blockers depends on their receptor selectivity. In those without intrinsic sympathomimetic activity, the heart rate is slowed, a decrease is seen in cardiac output, and an increase is noted in peripheral vascular resistance. Bronchospasm may also be

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the cause. Typical side effects seen with these agents include fatigue, erectile dysfunction, dyspnea, cold extremities, cough, drowsiness, and dizziness. These agents tend to increase the triglyceride level and decrease the HDL level but have little effect on blood glucose levels. Beta-blockers should not be used in patients with sinus bradycardia, second- or third-degree heart block, cardiogenic shock, cardiac failure, and/or severe COPD/asthma.

Central Acting Drugs

Methyldopa, clonidine, guanfacine, and guanabenz are central alpha-2 agonists. These agents act to decrease dopamine and norepinephrine production in the brain, resulting in decreased sympathetic nervous activity throughout the body. BP declines with the decrease in peripheral resistance. Methyldopa is unique in its adverse effect profile as it can induce autoimmune disorders such as those with positive Coombs' and antinuclear antibody (ANA) tests, hemolytic anemia, and hepatic necrosis. The other agents can lead to sedation, dry mouth, and dizziness. Importantly, abrupt clonidine withdrawal can lead to rebound hypertension.

Alpha-Blockers

Alpha-1 receptor blockers, such as prazosin, terazosin, and doxazosin, block the uptake of catecholamines by smooth muscle cells. In the peripheral vasculature, this results in vasodilation. A marked reduction in BP may be noted with the first dose of these drugs; therefore, it is recommended they be started at low doses and slowly titrated upward. Side effects of these agents include dizziness, sedation, nasal congestion, headaches, and postural effects. They have no effect on lipid levels, glucose, exercise tolerance, or electrolytes. These agents are probably best reserved for men with hypertension and comorbid BPH symptoms.

Vasodilators

Hydralazine and minoxidil dilate peripheral arterioles, resulting in a fall in BP. Several other responses simultaneously occur including a sympathetic reflex which leads to increased heart rate, renin and catecholamine release, and venous constriction. The kidneys retain sodium and water. Side effects include tachycardia, flushing, and headache. A beta-blocker and a loop diuretic are usually used with these drugs to minimize side effects. These agents are used mainly for resistant hypertension.

Special Considerations

Hypertensive Emergency

A hypertensive emergency is described as a severe elevation in BP accompanied by evidence of impending or progressive target organ dysfunction. Note that the actual BP measurement is not likely as important as the rate of the rise in blood pressure since patients with chronic hypertension often tolerate higher BP levels than normotensive individuals.

The most common origin of hypertensive emergency is an abrupt increase in BP in patients with chronic hypertension, which may be related to medication noncompliance. Hypertensive emergency can also be caused by certain medications or substances. Examples include withdrawal syndrome from antihypertensives including clonidine and beta-blockers as well as stimulant intoxication with cocaine, methamphetamine, and phencyclidine (PCP).

Clinical manifestations of target organ damage usually involve derangements in the neurologic, cardiac, or renal systems. The patient with hypertensive emergency may present with encephalopathy, pulmonary edema, myocardial infarction, or unstable angina.

Upon presentation, a focused physical exam should include repeated BP recording in both arms. Direct ophthalmoscope exam should be completed with special attention to look for papilledema. A brief neurologic examination should be done to assess for focal deficits and to assess for altered mental status. The cardiac and pulmonary examination should be complete with attention to possible arrhythmias and pulmonary edema. Abdominal exam should focus on palpating for abdominal masses and tenderness as well as auscultation for abdominal bruits. Peripheral pulses should be palpated.

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The immediate goal when treating hypertensive emergency is to reduce the systolic by no more than 25%, within the first hour, and if the patient is then stable, to 160/100–110 mm Hg over the ensuing 2–6 h [10]. Treatment should be more aggressive for certain patients, however. For adults with a compelling condition like severe preeclampsia/eclampsia or pheochromocytoma crisis, blood pressure should be reduced to less than 140 mm Hg during the first hour. For patients with aortic dissection, blood pressure should be reduced to less than 120 mm Hg in that same time [10]. The selection of an antihypertensive agent is an individualized one. Beta-blockers, vasodilators, dopamine agonists, and calcium channel blockers are all potential agents. The selection of which medication should be based on the drug's pharmacology, the underlying pathophysiology of the patient's hypertension, the degree of target organ damage, the rate of desired blood pressure decline, and the presence of comorbidities [10].

Hypertension Treatment in Older Adults

While current JNC 8 guidelines and the USPSTF recommend treating patients over age 60 to a blood pressure of <150/90, several studies are in support of tighter blood pressure control in order to reduce cardiovascular events. The Hypertension in the Very Elderly Trial (HYVET) was one of the first large-scale clinical trials to establish the benefit of lowering blood pressure in patients 80 years and older [20]. The Systolic Blood Pressure Intervention Trial (SPRINT) was a sentinel clinical trial that compared cardiovascular outcomes in patients with increased cardiovascular risk who were randomized to an intensive blood pressure goal of less than 120 mm Hg or a standard blood pressure goal of less than 140 mm Hg [21]. A subanalysis of the SPRINT trial was completed on patients over the age of 75 which also supported more intensive blood pressure control as a way of preventing cardiovascular events, even in frail older adults. On the other hand, several cohort studies of adults 80 years of age and over have shown that participants with low blood pressure at baseline had higher all-cause mortality rates [22–25]. These findings suggest that lowering BP among the oldest-old might be harmful. While these findings could be related to patient selection, frailty or other poor health indicators, or confounding causality, the current recommendations for adults over the age of 75 remain to control blood pressure to <150/90 mm Hg.

"Race"-Based Treatment

JNC 7 was one of the first hypertension guidelines to mention race-specific recommendations for treatment of high blood pressure. In the JNC 7, thiazide diuretics were considered as the first-line therapy for black patients [6]. The JNC 8 guidelines were similar in the recommendation of thiazide-type diuretics being considered first line, but also added that calcium channel blockers should be used as the antihypertensive treatment of choice in the general black population, including those with diabetes [7]. The authors of this chapter chose to deemphasize these race-specific recommendations since a large body of anthropological and contemporary genetic evidence suggests that "race" is a social construct, not a biological one. Insights into genetic variation support the notion that humans are essentially the same, and there is greater variation within identified racial groups than across groups [26]. In addition, while there is ample evidence from clinical trials that demonstrate differences in cardiovascular outcomes among populations in the United States, the participation of various racial/ethnic groups other than white populations in multiple trials has been inconsistent, inadequate, or not measured [27]. Since there are multiple complex factors that affect blood pressure control in patients of all racial/ethnic backgrounds (i.e., socioeconomic standing, lifestyle, clinical inertia, and even discrimination or bias), the interpretation of medical literature and guidelines utilizing "race" is challenging. Until future studies analyze concepts of ancestry, which incorporates ethnicity, geography, and genetics, clinicians should take care with "race"-based recommendations, and instead approach patients in

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an individualized manner, prioritizing care that is simultaneously culturally aware and evidence based.

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Ischemic Heart Disease

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General Principles

Ischemic heart disease (IHD) refers to the condition of inadequate blood supply to the myocardium. It is also commonly referred to as heart disease, coronary heart disease (CHD), or coronary artery disease (CAD). From 2013 to 2016, the total number of people age 20 and older in the United Sates affected by IHD was estimated to be 18.2 million [1]. Each year about 605,000 Americans have their first myocardial infarction (MI), with more than 200,000 experiencing a subsequent event [1]. While deaths from IHD have declined since 2000, it remains the leading killer of both men and women [1, 2]. In addition to the loss of life, IHD has a large financial impact. The National Heart, Lung, and Blood Institute estimates a loss of 218 billion dollars in 2014 including loss of productivity [1].

Angina pectoris, or simply angina, refers to the chest pain that occurs when myocardial oxygen supply cannot keep up with demand. Most patients with IHD experience angina. Thus, the evaluation of angina or chest pain is ultimately what leads to the diagnosis in most instances. Acute coronary syndrome (ACS) is a term used

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to describe a range of conditions associated with sudden, reduced blood flow to the heart [3]. This chapter will review the diagnosis of IHD when patients present with chest pain, distinguish between the acute coronary syndromes, and describe the management of acute coronary syndrome as well as stable IHD.

Diagnosis

History

The first task when evaluating a patient with chest pain is to quickly establish whether it is secondary to a life threatening cause such as an acute MI or other emergent cause such as pulmonary embolism, aortic dissection, or tension pneumothorax, to list a few. It is important to note that few patients with chest pain seen in the primary care setting have emergent or cardiac causes. Most patients presenting with chest pain in the outpatient setting have musculoskeletal (36%), gastrointestinal (19%), or anxiety-related causes (7.5%) [4]. These prevalence estimates reinforce the need for confidence in understanding the presentations of IHD.

The clinical history is one of the most important tools in the evaluation of the patient presenting with chest pain. Typical angina is described as substernal chest pain or discomfort that is provoked by exertion or emotional stress and relieved by rest or nitroglycerin. Its onset is usually not abrupt, and its duration is usually only a few minutes. When the chest pain has two of these criteria, it is classified as atypical angina. Nonanginal chest pain has only one of these clinical features [5]. While certain characteristics of the chest pain history are associated with increased or decreased likelihoods of a diagnosis of ACSs or MI, none of them alone or in combination are sufficient to diagnose a cardiac etiology [6]. Angina can be specified further by the level of exertion needed prior to onset. The tables below outline a general perspective on how to think about chest pain of possible cardiac origin (Tables 1 and 2).

As mentioned above, it is important to note that atypical angina or nonanginal chest pain does not mean that IHD is not the cause, only that the pain is much less characteristic. Pretest probability for IHD is assessed by taking into consideration the type of chest pain (typical angina, atypical angina, nonanginal) and a patient's age and sex (Table 3). Additional pretest estimates may take into consideration changing demographics, comorbidities, and improvements in imaging and diagnostics [8]. While pretest probability is helpful, clinicians should not solely rely on this estimate to determine need for further evaluation of a patient with chest pain.

Gender differences make correlating symptoms to anatomic causes challenging. The WISE (Women's Ischemic Syndrome Evaluation) study highlighted that women ultimately diagnosed with IHD did not have typical angina 65% of the time [10]. Women also have a higher likelihood of ACS related to *microvascular etiology* rather than to stenosis of coronary arteries [11]. Finally, some patients lack the chest discomfort and are thus characterized as having silent ischemia.

Table 1 Clinical criteria of angina

	Typical	Atypical	Nonanginal
Angina	Substernal chest pain or discomfort; may radiate to arm or jaw. Provoked by exertion or emotional stress. Relieved by rest and/or nitroglycerin.	2 of the three features of typical chest pain. Pain is often located elsewhere, right side or left side of chest, for example.	1 of the three features. Note that "nonanginal" does not necessarily mean not of cardiac origin.

Table 2 Clinical criteria of stable versus unstable angina

	Stable	Unstable [7]
Angina	Symptoms of angina provoked by a consistent level of exertion or emotional stress. Relieved by rest.	Unprovoked chest pain or provoked by less exertion than previously. Generally not relieved by rest or medications. Lasting for longer periods of time.

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Table 3 Estimating pretest probability of ischemic heart disease, Diamond Forrester model [9]

	Men			Women		
Age range	Nonanginal	Atypical	Typical	Nonanginal	Atypical	Typical
30–39 years	5.2	21.8	69.7	0.8	4.2	25.8
40–49 years	14.1	46.1	87.3	2.8	13.3	55.2
50–59 years	21.5	58.9	92.0	8.4	32.4	79.4
60–69 years	28.1	67.1	94.3	18.6	54.4	90.6

Other important symptoms to inquire about include pain radiating to arm(s) or jaw, epigastric pain, dyspnea, and any association of the pain with nausea, diaphoresis, or syncope [12]. Such clinical features increase the probability of a myocardial infarction in patients presenting with chest pain. Interestingly, pain radiating to both arms is the clinical feature that has the strongest positive likelihood ratio (approximately 7) for acute MI [13]. Pain that is pleuritic, sharp, or positional tends to lower the likelihood of MI as the etiology [14].

Obtaining a thorough past medical history is extremely valuable when assessing a patient for possible IHD. A history of hypertension, hyperlipidemia, diabetes, and any prior cardiovascular events should be noted.

ACS, in addition to unstable angina (UA), includes ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI). In patients with previously stable angina, a change of chest pain from baseline in terms of increase in frequency, new occurrence with lower levels of activity, or increase in length of symptoms also is consistent with UA [3]. UA and MI cannot be differentiated by history alone. The use of electrocardiogram and cardiac biomarkers (discussed below) is essential to distinguishing amongst these clinical entities.

Physical Exam

The physical exam is less helpful in the diagnosis of IHD. The physical exam of the patient presenting with chest pain that may represent underlying IHD begins with an assessment of vital signs. Note the pulse and blood pressure. Significant hypotension may be a manifestation of MI. Diaphoresis may be present, and sweating in association with typical or atypical angina is a much better predictor of STEMI or NSTEMI than UA [13]. A third heart sound or pulmonary crackles on auscultation also would be concerning for possible MI [14]. Tenderness or reproducibility of chest pain on chest wall palpation argues against IHD as a diagnosis but does not necessarily rule it out [15].

Electrocardiogram and Biomarkers

The electrocardiogram (ECG) is a critical component of the evaluation of chest pain suggesting IHD, whether stable or possible ACS. A pathologic Q-wave is indication of prior MI. ECG abnormalities that may indicate myocardial ischemia include changes in the PR segment, the QRS complex, and the ST-segment. In the setting of possible ACS, a careful evaluation of ECG changes can assist in estimating time of the event, amount of myocardium at risk, patient prognosis, and appropriate therapeutic strategies. ST segment elevation found on an ECG is the hallmark sign of an acute STEMI [12]. The ECG alone is often insufficient to make the diagnosis of an acute MI, and the sensitivity and specificity of ECG are increased by serial assessments [16]. ECG changes such as ST deviation may be present in other conditions, such as left ventricular hypertrophy, left bundle branch block, or acute pericarditis. Note that in addition to patients diagnosed at the time of presentation of their chest pain, each year an additional 170,000 Americans experience a "silent" MI [1].

Like the ECG, cardiac biomarkers are an important extension of the history and physical examination in the evaluation of the patient with

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possible ACS. They are not part of the evaluation of patients with stable IHD. Cardiac troponins, the gold standard, are biochemical markers of active or recent myocardial damage. Increases in cardiac biomarkers, notably conventional cardiac troponins (cTnI or cTnT), or the MB fraction of creatinine kinase (CKMB), signify myocardial injury leading to necrosis of myocardial cells. Patients may present for evaluation before cTn values elevate, and others may have values that do not change on serial measurement [17]. High-sensitive troponin (hsTn) may assist with ruling out MI when not elevated. Elevated hsTn may also signal ischemia without infarction [17].

Troponin levels should be measured on initial assessment, within 6 h after the onset of chest pain, and in the 6–12 h time frame after onset of pain. In addition, it is important to understand that elevations in troponin may be seen for up to 14 days after the onset of myocardial necrosis. The preferred cardiac biomarker is troponin, which has high clinical sensitivity and myocardial tissue specificity [18]. If troponin concentrations are unavailable, then CKMB should be measured. Ideally, both troponin and CKMB should be obtained during evaluation for ACS due to the different concentrations of these biomarkers over time and the added diagnostic value of serial testing.

However, elevated cardiac biomarkers in and of themselves do not indicate the underlying mechanism of injury and do not differentiate between ischemic or nonischemic causes. There are several clinical conditions that have the potential to result in myocardial injury and cause elevations in cardiac biomarkers, including acute pulmonary embolism, heart failure, end stage renal disease, and myocarditis [19]. As a result, cardiac biomarker elevations cannot be utilized in isolation to make a diagnosis of MI.

Stress Testing and Cardiac Imaging

In the evaluation of a patient with possible IHD who is otherwise stable and not experiencing ACS, the first step before ordering or conducting a stress test is to gauge clinical utility. For patients with a low pretest probability, a stress test is unlikely to be helpful. The sensitivity and specificity of a standard exercise tolerance test varies depending on the extent of disease (e.g., >70% stenosis), but in general has a sensitivity of approximately 50–65% and specificity of approximately 75–85% [20, 21]. For example, a 36-year-old woman with atypical chest pain has an estimated pretest probability of 4%. If an exercise tolerance test is positive, her posttest probability of having IHD is only about 9–10%; and if the test is negative, her posttest probability of having IHD is about 2%. The test is most useful for people with a moderate pretest probability, although the testing range spans from 10% to 90%. For people with a high pretest probability, a negative stress test does not reduce the post-test probability sufficiently. In addition to the predicted posttest utility of stress testing, the clinician should take into consideration other factors such as clinical presentation, comorbidities, and other variables in considering stress testing and further diagnostic workup.

Before embarking on standard exercise tolerance testing, it is also important to know that the patient can exercise sufficiently for the test. An ECG should be obtained prior to ordering the stress test to make sure that there are no baseline ECG abnormalities that will make interpretation of the stress test difficult. Patients with a bundle branch block (especially left) or irregularities in the ST segment (e.g., due to digitalis or strain pattern) are not candidates for standard exercise tolerance testing.

There are many alternatives to a standard exercise tolerance stress test, and when considering concomitant imaging, the decision making can seem complicated. Factors to consider are the patient's ability to exercise, previous history of MI, baseline ECG including any rhythm abnormalities. The most common alternative to standard exercise tolerance testing is radionuclide perfusion imaging. It can be accomplished with or without exercise. A radionuclide (e.g., technetium-99 m sestamibi) is injected intravenously and its uptake by the myocardium is compared via imaging during rest and at peak exercise. For patients unable to exercise, adenosine or dipyridamole is used to dilate the coronary arteries and induce a relative

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difference between stenotic and nonstenotic vessels. Sensitivity and specificity are greater with perfusion testing (approximately 75% and 85%, respectively). Stress echocardiography is another test that can be used to evaluate for possible IHD. Areas of the myocardium that are not perfused will exhibit a wall-motion defect. Like radionuclide imaging, stress echocardiography can be performed with or without exercise, the latter method using dobutamine.

Coronary Angiography

Patients with a positive stress test or those with a high pretest probability or for whom the diagnosis remains equivocal should be referred for possible coronary angiography. Coronary angiography is the gold standard for diagnosing coronary artery disease, and depending on the findings, therapeutic interventions can be accomplished simultaneously.

Management

Acute Coronary Syndrome

Initial management of ACS consists of identifying whether a patient should be managed with an early invasive strategy versus an initial conservative strategy. Early risk stratification should take into account a patient's age and medical history, physical exam, ECG, and cardiac biomarker measurements [3]. A risk assessment tool can be used to predict the patient's risk of recurrent ischemia or death following an ACS event. The Thrombosis and Myocardial Infarction (TIMI) risk score is a scoring system for unstable angina and NSTEMI that incorporates seven variables upon hospital admission and has been validated as a reliable predictor of subsequent ischemic events (Table 4) [3].

For patients presenting with a STEMI with symptom onset within the prior 12 h, reperfusion therapy should be considered [22]. Percutaneous coronary intervention (PCI) is the recommended method of reperfusion when it can be performed with the goal of time from first medical contact to device time of less than or equal to 90 min [22].

Table 4 The thrombosis and myocardial infarction (TIMI) risk score for UA/NSTEMI [3]

Baseline characteristics	TIMI risk score (points)	Rate of composite endpoint (%)[a]
1 point for each of the following: Age ≥ 65 years At least 3 risk factors for IHD[b] Prior coronary stenosis ≥50% ST segment deviation At least 2 anginal events in last 24 h Use of aspirin in last 7 days Elevated serum cardiac biomarkers[c]	0–1	4.7
	2	8.3
	3	13.2
	4	19.9
	5	26.2
	6–7	40.9

[a]All-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization through 14 days after randomization
[b]Risk factors include family history of IHD, hypertension, hypercholesterolemia, diabetes, or being a current smoker
[c]CKMB fraction and/or cardiac-specific troponin level

If patients are unable to get to a PCI-capable hospital within 120 min of a STEMI, then fibrinolytic therapy should be administered within 30 min of hospital arrival, provided there are no contraindications. The benefits of an early invasive strategy for patients initially presenting with NSTEMI or unstable angina are less certain. A meta-analysis was inconclusive in regard to survival benefit associated with early (typically <24 h) vs. delayed invasive strategy in patients presenting with NSTEMI [23]. However, early invasive coronary angiography is recommended in NSTEMI/unstable angina patients who have refractory angina or hemodynamic or electrical instability [24]. Early invasive strategy is reasonable for higher risk NSTEMI/UA patients previously stabilized who do not have serious comorbidities (e.g., liver or pulmonary failure, cancer) or contraindications to the procedure [old 18 new 25]. There is no clear benefit to PCI for individuals with stable angina, and studies show that medical management is just as effective in preventing mortality [25].

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Antiplatelet therapy is a foundational in the management of ACS because it reduces the risk of thrombosis [24]. Well-established antiplatelet therapies in the management of ACS include aspirin, adenosine diphosphate P2Y12 receptor antagonists, and glycoprotein IIb/IIIa inhibitors. Aspirin should be started as soon as possible after an ACS event with an initial loading dose of 162 mg to 325 mg, unless contraindicated. Aspirin should be continued at a dose of 81-mg daily. A P2Y12 antagonist should be added to aspirin for patients with ACS who are medically managed as well as those undergoing PCI [23, 24]. P2Y12 receptor antagonists frequently used in the management of ACS include clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brillinta) [26–29]. Triple antiplatelet therapy accomplished by adding GP IIb/IIIa inhibitors has been shown to be efficacious when used during PCI in reducing ischemic complications. However, triple antiplatelet therapy has also been associated with an increased bleeding risk [24].

Parenteral anticoagulants (unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, or bivalirudin) are used in combination with antiplatelet agents during the initial management of ACS. The choice of anticoagulant agent is dependent upon the initial management strategy and the recommended duration of therapy varies based on the chosen agent [22, 24].

For patients presenting with unstable angina, NSTEMI, or STEMI, oral beta-blocker therapy should be initiated within 24 h of the onset of the event unless the patient has evidence of low-output state, signs of heart failure, increased risk for cardiogenic shock or other contraindications to therapy [3]. The use of intravenous beta-blockers is reasonable in patients who are hypertensive and do not have contraindications. Beta-blockers decrease cardiac work and reduce myocardial oxygen demand by reducing myocardial contractility, sinus node rate, and AV node conduction velocity. Beta-blocker should be continued in the post-MI setting unless contraindicated or not tolerated. The duration of benefit of long-term oral beta blocker therapy is uncertain, but many clinicians choose to continue beta blockers indefinitely. If patients are experiencing side effects from beta blocker use, it may be reasonable to discontinue therapy at least 1 year after an MI [30]. For patients who are unable to take beta blockers and experience recurrent ischemia, consideration should be given to starting a non-dihydropyridine calcium channel blocker (i.e., verapamil or diltiazem) [3, 22].

As long as no contraindications exist, an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) should be initiated within the first 24 h of patients presenting with ACS who have pulmonary congestion, heart failure, STEMI with anterior location, or left ventricular ejection fraction (LVEF) $\leq$ 40% [3, 22]. ACE inhibitors have been shown to reduce mortality in a broad spectrum of patients following MI, including those with and without LV dysfunction [31–36]. Patients with stable CAD who are not medically optimized (i.e., cannot tolerate a beta blocker or statin), who are not able to be re-vascularized, and/or who have poorly controlled diabetes have shown mortality benefit with continued treatment with ACE inhibitors [37]. When initiating inhibitors of the renin-angiotensin system, it is important to monitor for adverse effects associated with these agents including hyperkalemia, elevations in serum creatinine, and hypotension.

Statin (HmG-CoA reductase inhibitor) therapy is recommended for all patients presenting with ACS who have no contraindications [22, 24]. High-intensity statin therapy following an ACS event was shown to confer an absolute risk reduction of 4% over 2 years compared with a moderate intensity statin for the composite endpoint of death from any cause, recurrent MI, UA requiring rehospitalization, revascularization, and stroke [38]. Statin therapy is beneficial following ACS even in patients with baseline low-density lipoprotein (LDL) cholesterol levels of $<$70 mg/dL [22, 24]. Recently published American College of Cardiology and American Heart Association Guidelines on treatment of cholesterol recommend high intensity statins (i.e., $\geq$ atorvastatin 40 mg daily or $\geq$ rosuvastatin 20 mg daily) for high-risk patients, which include patients who have an ACS

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event [39]. Lower dose statins can be considered if patients are >75 years old or if patients cannot tolerate high intensity statins. Ezetimibe and then PCSK9 inhibitors may be utilized in very high risk patients who have LDL levels that remain at 70 or above [39]. Other medications such as colchicine are showing promise to prevent further ischemic events after MI [40].

Stable Ischemic Heart Disease

Stable ischemic heart disease represents an established pattern of angina, a history of myocardial infarction, or the diagnosis of coronary artery disease on catheterization. The goals of managing stable IHD are to prevent progression of disease and reduce the likelihood of cardiovascular disease events (secondary prevention), ultimately reducing premature mortality. The "ABCss" of management are shown in Table 5.

Low-dose aspirin (typically 81-mg) is recommended for all patients for secondary prevention unless it is contraindicated (e.g., allergy) or poorly tolerated. Aspirin inhibits cyclooxygenase, and the resultant reductions in prostaglandin and thromboxane-A prevent platelet aggregation. Numerous studies have demonstrated the benefit of aspirin for secondary prevention.

Control of blood pressure is important in the management of IHD. Recent evidence-based guidelines recommend initiation of treatment for hypertension at blood pressure > 140 mm Hg systolic and/or > 90 mm Hg diastolic in patients with diabetes, CKD, or in patients younger than 60 years old without these comorbidities [33]. These new guidelines support permissive elevation of systolic blood pressure to 150 mm Hg prior to initiation of therapy in patients 60 years and older. See ▶ Chap. 79, "Hypertension" for further discussion of BP-lowering.

Cholesterol Lowering. The ACC/AHA Lipid Guidelines support use of a high-dose statin in all patients less than 75 years old who will tolerate this treatment [39]. The LDL goals seen in previous guidelines are no longer recommended. Consider at least a moderate dose statin in patients older than 75 [39]. Statins are the preferred treatment, but for patients who do not tolerate them or have other risk factors that may classify them as very high risk, ezetimibe, PCSK9 inhibitor, or a bile acid sequestrant can be considered. Niacin and fibrates can be prescribed for patients with elevated triglycerides [39].

Patients with IHD should be counseled to make smoking cessation a priority. See ▶ Chap. 6, "Clinical Prevention" for information on strategies and clinical interventions that may help patients become smoke free.

Options for antianginal therapy include beta-blockers, nitrates and calcium channel blockers. Beta-blockers are the first-line recommendation for control of angina. By reducing myocardial oxygen demand, they reduce the frequency of chest pain episodes and improve exercise tolerance. In addition to their benefit for symptom

Table 5 Management of stable ischemic heart disease

	Recommendation	Comment
Aspirin	81-mg daily unless contraindicated	Clopidogrel can be used for patients allergic to aspirin
Blood pressure lowering medication(s)	Goal BP < 140/90 mm Hg for most patients	Beta-blocker recommended as part of regimen for post-MI patients
Cholesterol lowering medication	Statin therapy	Use at highest tolerated dose
Smoking cessation	Any patient who smokes should be provided recommendation, counseling and resources to quit	
Symptom management	Control angina symptoms with beta-blocker, nitrates, and/or calcium channel blocker	Beta-blocker is first-line; calcium channel blocker should be long-acting nondihydropyridine or dihydropyridine (avoid nifedipine); long-acting nitrate can be added to help manage chronic angina

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control, beta-blockers help prevent reinfarction and reduce mortality in patients who have suffered an MI. When beta-blockers are contraindicated or not effective as monotherapy, a nitrate or calcium channel blocker can be used.

Sublingual nitroglycerin or nitroglycerin spray is provided for relief of acute episodes of IHD related chest pain. These preparations can also be used a few minutes before activity to prevent effort-induced angina. A long-acting nitrate (e.g., isosorbide mononitrate) can be provided as a supplement to beta-blocker or calcium channel blocker for controlling chronic angina. Nitrate tolerance is minimized by having a nitrate-free interval of about 12 h.

Anolazine can be considered as an add-on for angina control. It is a sodium channel blocker that reduces oxygen demand by decreasing tension during ventricular relaxation. The medication can be a useful when angina is not controlled with the above strategies or can be prescribed instead of beta-blockers if beta-blockade is contraindicated or poorly tolerated [5]. Ranolazine can be used in patients with bradycardia or low blood pressure.

Lifestyle modifications for all patients include weight loss if overweight, regular physical activity, and an eating plan that is low in saturated fats, trans fats, and cholesterol [5]. Referring a patient to a dietitian may be reasonable.

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Cardiac Arrhythmias

81

Cecilia Gutierrez and Esmat Hatamy

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The electrical activation of heart muscle follows a precise and organized pathway which ensures that contraction and relaxation occur in an efficient way to support effective circulation. Arrhythmias result from an abnormal electrical activation of the heart which may lead to an abnormal rhythm, rate,

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or both in the heart cycle. While some arrhythmias are benign and pose no significant cardiovascular compromise, others degrade the mechanical pumping activity and lead to hemodynamic compromise and, in some cases, to collapse and/or death.

Arrhythmias are commonly seen in primary care, and many are diagnosed and managed by primary care physicians, either alone or along with a cardiologist. Although more common among the elderly and those with heart disease, they must be considered in the differential diagnosis of all patients presenting with syncope, lightheadedness, palpitations, fatigue, dyspnea on exertion, and shortness of breath. The main goal in evaluating patients is to first assess cardiopulmonary stability and, in life-threatening situations, activate the emergency response system. In stable patients the work-up focuses on identifying the arrhythmia, its cause(s), its effect on cardiac function, and treating it to improve patients' symptoms and reduce morbidity and mortality.

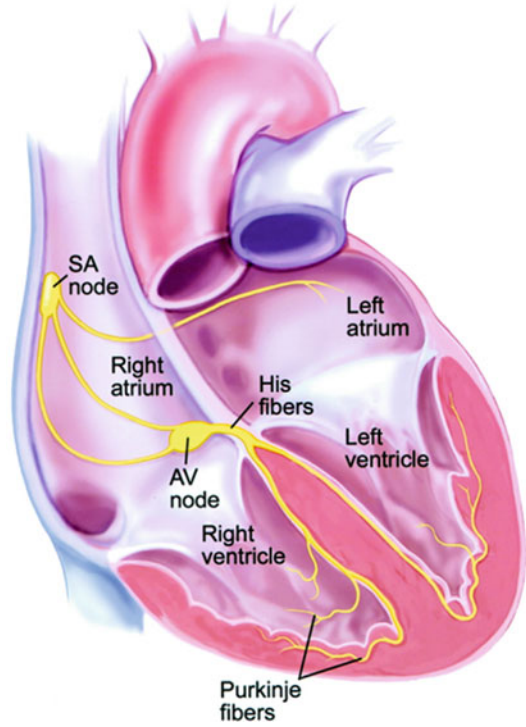


Fig. 1 Diagram of the heart and the electrical conduction system of the heart (From Wang and Estes [1])

Electrophysiology of the Heart

The heart generates its own electrical impulse, an action potential (AP) transmitted through specialized cells and conductive fibers to activate myocardial cells to contract and relax in a highly coordinated fashion. This determines heart rate and rhythm.

In a simplified view, at the molecular level, the generation of the AP is due to unstable transmembrane potential caused by a slow sodium (Na+) leak into the cells, depolarizing the membranes until the threshold that triggers an AP is reached. Cardiac cells have several voltage-gated ion channels, and the in- and outflow of mostly Na, K, and Ca ions through these gated channels (fast and slow) play key roles in generating the AP and repolarizing cell membranes. Through the cycle, cells exhibit absolute and relative refractory periods. Sympathetic and parasympathetic fibers innervate the heart and modulate cardiac function.

Figure 1 [1] shows a schematic and simplified view of the normal electrical conduction system. The AP originates at sinoatrial node (SA), a group of specialized cells in the upper posterior wall of the right atrium. It is transmitted to the atria and to the atrioventricular node (AV), a group of cells in the posterior region of the atrial septum. In the AV node, the impulse is delayed, allowing atrial contraction to occur before the ventricular activation. The AV node transmits the impulse through the bundle of His, fast-conducting fibers in the upper interventricular septum, which splits into two branches, right and left. Then the impulse continues through the Purkinje fibers, which transmit it to all ventricular cells, resulting in ventricular contraction and ejection of blood into the circulation. Although the AV node, bundle of His, and Purkinje can act as pacemakers, the SA node has the highest intrinsic rate of depolarization, and it serves as the pacemaker. At rest, the SA node triggers APs at a rate of 60 to 100 times per minute. In an ECG this pattern is seen as regular waves known as P, QRS, and T waves, which is normal sinus rhythm (NSR).

Detailed knowledge of the variety of ion channels and their electrophysiology is beyond the

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scope of this chapter. However, it is essential to point out some highlights which have clinical and pharmacologic significance.

Various types of ion channels exist in myocytes. Some channels are present in all cells, while others only on certain cells, or preferentially on specific areas of the conduction system. Although the major ions involved are Na, K, and Ca, other ions may also play a role and/or serve to modulate their responses. Some channels are fast, while others are slow; some are voltage gated, and some are modulated by local current across gap junctions with adjacent cells, while others are affected by local currents within the cells (e.g., across their sarcoplasmic reticulum), or via special proteins, ion transport mechanisms, and other intracellular signals. Some channels are up- or downregulated, and some have mutations (leading to familial channelopathies). Some channels are transient responding to immediate changes in the cells in ways to achieve homeostasis, while others undergo permanent changes due to long-standing chronic ischemia, scarring, and remodeling.

Three main mechanisms have been identified as the causes of arrhythmias: increased automaticity, triggered activity, and re-entry. Re-entry is the most common cause of arrhythmias. It occurs when the normal electrical impulse does not dissipate and re-excite cardiac cells after the refractory period.

Arrhythmias are described according to where they originate (in the atria or ventricles, along the multiple sites of the electrical conduction system, or on myocardial cells); according to their effect on heart rate (HR) (fast, tachyarrhythmias, $>$ 100 beats per minute, or slow, bradyarrhythmias, $<$ 60 beats per minute); and according to their effect on heart rhythm (regular versus irregular patterns). All these characteristics define a unique pattern in the ECG.

Evaluation of Patients with Arrhythmia

History and Physical Exam (H&P)

Although studies have shown poor correlation between symptoms and actual arrhythmias, the H&P helps to identify potential causes, risk factors, and comorbidities. Elements of the history must consider both cardiac and non-cardiac causes of arrhythmia. As usual, it must include onset, patient's description of symptoms, duration, aggravating and alleviating factors, severity, and course of symptoms. The review of systems must inquire about shortness of breath, palpitations, dizziness, edema, orthopnea, paroxysmal nocturnal dyspnea, fatigue, lightheadedness, chest pain, syncope, orthostatic hypotension, symptoms of sleep apnea, pedal edema, new medications (prescribed or over the counter), herbal and other supplements, symptoms of thyroid disease, and recent illnesses. The social history provides information about the use of recreational drugs, alcohol, and diet pills as possible causes or contributors. Table 1 presents the most common causes of arrhythmias. Rare conditions such as infiltrative heart diseases, pheochromocytoma, and other endocrine conditions must be considered. All patients must have a complete PE, vital signs, and BMI. The cardiovascular exam should include inspection, palpation, percussion and auscultation of the heart, assessment of heart rate and rhythm, presence of murmurs, carotid bruits, patient's JVD, peripheral pulses, and edema.

Table 1 Most common causes of arrhythmias

Cardiac	Non-cardiac
CAD: Myocardial ischemia or infarction	Pulmonary disease
Heart failure	COPD, PE, pneumonia
Structural heart disease:	Cor pulmonale
Congenital or acquired	Thyroid disease
Dilated cardiomyopathy	Drug toxicity
Ventricular hypertrophy	Antiarrhythmics
Valvular disease	Beta agonist inhalers
Atrial septal defect	Lithium
Ebstein anomaly	Drugs that increase
Epicardial, myocardial, and endocardial diseases:	QT interval
Infectious, injury, or drug toxicity	Electrolyte abnormalities
Iatrogenic	Recreational drugs
Post-cardiac catheterization	Diet pills
Post-cardiac surgery	Collagen vascular disease
Post-ablation	Infiltrative disease
Post-ICD placement	Hypothermia

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Evaluation of Cardiac Arrhythmia

Because patient symptoms often do not correlate with actual arrhythmias and the H&P cannot characterize the arrhythmia, the first step is to get an ECG. The ECG provides immediate information of the HR and rhythm and changes in P wave, PR interval, QRS complexes, ST segment, and T waves. Since a normal ECG cannot capture a paroxysmal arrhythmia, a Holter monitor (24-h recording) or an event monitor (7–30 days recording) may be required. In some cases a long-term implantable loop recorder may be necessary [2]. An echocardiogram is also needed to evaluate heart function and assess for possible structural diseases.

Initial blood tests include a complete blood count with differential, a comprehensive metabolic panel, magnesium, lipid panel, and TSH. Additional tests may be necessary depending on the patient's H&P and risk factors. These include stress echocardiogram, nuclear perfusion imaging or cardiac catheterization for ischemia or coronary artery disease, table tilt test for vasovagal syncope, drug screen (if suspected), and urine vanillylmandelic acid and serum metanephrine for evaluation of possible pheochromocytoma.

Treatment Options for Cardiac Arrhythmia

Several options are available to treat arrhythmias. They include cardioversion, drugs with AV nodal suppression, antiarrhythmic drugs acting on different ion channels, radiofrequency ablation, pacemakers, defibrillators, and surgery. Based on best evidence from clinical trials, the most updated knowledge of pharmacology and pathophysiology, the American Heart Association, the American College of Cardiology, the European College of Cardiology, and the Heart Rhythm Society, AHA/ACC/ECC/HRS, have developed guidelines for the evaluation and treatment of arrhythmias [3–8]. These guidelines are frequently revised and updated to include latest knowledge, and they provide a framework for a discussion with patients and their families about treatment options. Therapeutic decisions also must reflect patients' preferences and choices. Prior to initiating a specific therapy, it is essential to identify and treat reversible causes of arrhythmias.

Cardioversion

It is the attempt to return the heart rhythm to NSR and can be achieved by an electrical current shock or by drugs. The goal is to override all abnormal electrical activity and synchronize the heart rhythm again. Unless done in an emergency basis, it requires preparation: IV access, continuous cardiac monitoring, sedation and/or anesthesia, resuscitation equipment, proper anticoagulation, normal electrolytes and short fasting, etc.

Electrical cardioversion is accomplished by delivering a direct current electric shock of 50–360 joules of energy. Shocks are delivered in synchrony with the R or S wave of the QRS complex, to avoid the relative refractory period and minimize triggering of other arrhythmias. One or more shocks may be necessary, starting at the lowest energy. The main indications for cardioversion are unstable or poorly tolerated narrow QRS complex tachycardias (atrial fibrillation (AF) or flutter) and ventricular tachycardia not responsive to drug therapy.

Pharmacological cardioversion and maintenance of NSR has been challenging due to limited long-term efficacy of drugs, the risk of triggering ventricular arrhythmias, and their long-term adverse side effects [3–5]. It is more successful in young patients with healthy hearts who have recently developed an arrhythmia. Most commonly used drugs include ibutilide (Corvert), flecainide (Tambocor), dofetilide, propafenone (Rythmol), and amiodarone (Cordarone, Nexterone, Pacerone). Contraindications for cardioversion include digitalis toxicity, multifocal atrial tachycardia, and suboptimal anticoagulation.

Antiarrhythmic Drug Therapy

Multiple drugs are available to suppress and treat arrhythmias, but their use is complex. Many drugs

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can trigger arrhythmias, some have serious short- and long-term adverse side effects, some require hospitalization to initiate therapy, some have limited long-term benefit, many have drug interactions, etc. Therefore, the patient should be referred to cardiology.

Antiarrhythmic drugs have various effects on ion channel function; most have more than one action. They may slow down, accelerate, or modify ion movement across cell membranes. They act at various phases of the AP and in unique ways along the specialized conduction system. Advances in electrophysiology and the development of new drugs led to the revision and expansion of the well-established Vaughan-Williams classification of antiarrhythmic drugs [9].

Table 2 presents the new drug classification, mode of action, indications, and contraindications for their use [3, 5, 9–12].

Class 0. This new class identifies drugs that have an effect on the automaticity of the SA node. Ivabradine is a drug that reduces heart rates in inappropriate sinus tachycardia [10].

Class I. These drugs block Na channels and therefore act on the depolarization phase of the cardiac AP. New classification identified a variety of Na^+ channels. Some of these drugs act early or late in the phase of the AP, while others act on voltage gated channels in the atria, Purkinje fibers and ventricles. They are further subdivided into four subclasses according to their effect on the duration of the AP [10]:

- Class Ia agents prolong the initial phase of the AP, thus delaying depolarization. They also increase the effective refractory period. Some examples are quinidine (Qualaquin), procainamide, and disopyramide (Norpace).
- Class Ib. These drugs shorten the duration of the AP by increasing repolarization. Some examples are lidocaine, phenytoin (Phenytek), mexiletine, and tocainide.
- Class Ic. These drugs have no effect on AP duration, but they significantly slow the initial depolarization of the AP and have no effect on refractory period. Some examples are encainide, flecainide (Tambocor), propafenone (Rythmol), and moricizine.
- Class Id. These drugs inhibit late Na + channels after the rapid initial repolarization phase. They shorten AP recovery and increase refractoriness. Examples include ranolazine, GS-458967, and F15845.

Class II. This classification includes drugs that have effect on sympathetic and parasympathetic activity, as well as drugs that act through cell membrane proteins, particularly G-proteins. They have ionotropic, chronotropic, and lusitropic (myocardial relaxation) effects on the heart:

- Class IIa include non-selective (carvedilol and propranolol) and selective (atenolol) $\beta 1$ adrenergic blockers. They inhibit Ca^{++} entry and release from the sarcoplasmic reticulum.
- Class IIb. In contrast to class IIa, these drugs stimulate Ca^{++} entry and release from the SR. An example is non-selective isoproterenol.
- Class IIc. These are drugs that act on muscarinic receptors via various G-proteins. An example is atropine.
- Classes IId and IIe. These drugs mediate their effects by inhibiting G-proteins. Examples are carbachol (IId) and adenosine (IIe) [10].

Class III. These drugs block K^+ channels, subtype and auxiliary subunits. They prolong repolarization and refractory period of myocytes:

- Class IIIa. They act on voltage-gated ion channels.
- Class IIIb. They affect specific K^+ channels via specific transmitters.
- Class IIIc. Act on K^+ channels affected by specific transmitters.

Class IV. These drugs are referred as calcium channel modulators. Overall, they delay conduction at the AV node, slowing HR. Subclasses in the surface of cells and within cell membranes (sarcoplasmic reticulum) have been identified. These channels have complex mechanisms affected by local currents, voltage, and Ca homeostasis and intracellular signals. Their activation at different times and sites and their

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Table 2 Antiarrhythmic drugs: classification, mode of action, indication, and contraindications

Drug classification		Medication name and MOA	Indications	Contraindications
0 **HCN channel blocker**		Ivabradine: ↓ SAN phase 4 depolarization, ↓ HR, possible ↓ AVN automaticity	Stable angina, chronic HF w HR > 70, potential use in tachyarrhythmia (IST)	Decompensated HF, SSS, BP < 90/50, third degree block (unless there is a pacemaker), severe liver disease
I **Sodium Channel Blockers**	Ia	Quinidine ↓↓ phase 0 slope	A-fib A-flutter VT, VF	HtoD, digitalis toxicity, complete AV dissociation, myasthenia gravis, Immune thrombocytopenia Thrombocytopenic purpura
		Procainamide ↑ AP duration	A-fib, VT, VF	HtoD, complete HB, second or third degree AVB SLE, torsades de pointes
		Disopyramide ↑ effective refractory period	VT	HtoD, cardiogenic shock, congenital prolonged QT Second or third degree block
		Ajmaline Changes shape and threshold of AP	Use as diagnostic drug to make diagnosis of BS No therapeutic use	Should not be used if BS diagnosis is clear
	Ib	Mexiletine ↓ AP duration	VT	HtoD, cardiogenic shock, second and third degree AVB, if no pacemaker is present
		Phenytoin (rarely used in arrhythmia) ↓ effective refractory period	VT secondary to digoxin	HtoD or other hydantoins Concomitant use with delavirdine or rilpivirine
		Lidocaine ↓ phase 0 slope	VF, VT	HtoD, use of local amide anesthetic
		Tocainide	VF, VT	HtoD, second and third degree AVB, HF, ↓ K, liver and kidney disease
	Ic	Flecainide ↓↓↓ phase 0 slope	PAF, ventricular arrhythmia PSVT, P-atrial flutter	HtoD, RBBB with left hemi-block without pacemaker, second and third degree AVB without pacemaker
		Propafenone ↔ AP duration	PSVT and PAF Without structural heart disease, VT	HtoD, bradycardia, BS, severe bronchospasm, COPD, cardiogenic

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Table 2 (continued)

Drug classification		Medication name and MOA	Indications	Contraindications
				shock, HF, electrolyte imbalance, marked hypotension. SSS and AVB without pacemaker
	Id	Ranolazine Affects the AP recovery, refractoriness, repolarization reserve, and QT interval	SA, VT, chronic angina in combination with other meds	Prolonged QT syndrome Partial contraindication/ caution: Severe impairment of kidney and liver
LII **Beta blockers** **Most commonly used**	IIa: Non-selective (NS) and selective (S) B1 inhibitors	NS: Carvedilol, nadolol, and propranolol (Inderal) S: Metoprolol, atenolol, bisoprolol, betaxolol, celiprolol, esmolol ↓ SAN and AVN and atrial /vent (ectopic) automaticity ↓ HR and conduction ↓ Chronotropy and ionotropy by inhibition of β1 receptor	VT, PVC, VF ST, A-fib, A-flutter, PAT	HtoD, ↓ BP or shock, severe bradycardia, HB >first degree (unless pacemaker), MI precipitated by cocaine, overt HF with pulmonary edema (start at low dose)
	IIb: Non-selective B adrenergic receptor activators	Isoproterenol ↓ RR and PR interval, stimulates both B1 snd B2 receptors, ↓ VR in SM, renal vascular bed	Cardiac arrest (when electric shock not available HB (not caused by AF, VT)	May have a deteriorating effect in injured or failing heart (↑ ox demand and ↓ effective perfusion) Should be used cautiously with inhaled anesthetic (halothane)
	IIc: Muscarinic receptor inhibitors Only atropine checked	Atropine anisodamine, hyoscine, and scopolamine ACI, which blocks the activity of the AC on M2R, ↑ the AVN conductivity, and ↓ SAN automaticity	Bradycardia, AV block in the setting of acute inferior MI, cardiac arrest/ Brady-asystole Vagal reaction to pain	Acute closed-angle glaucoma
	IId: Muscarinic receptor activators	Carbachol, pilocarpine, methacholine, and digoxin ↓ SAN automaticity, AVN conduction and re-entry	Sinus tachycardia and SV tachyarrhythmias	Asthma, incontinence, peptic ulcer disease, coronary insufficiency Do not use methacholine in

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Table 2 (continued)

Drug classification		Medication name and MOA	Indications	Contraindications
				hypertension, pregnancy, epilepsy
	IIe: Adenosine A1 receptor activators	Adenosine acts as an ARI MOA: ↓ conduction in AVN, interrupt re-entry pathway	SVT, WPW syndrome	Sinus bradycardia, SSS, Second and third degree heart block in the absence of a functioning pacemaker
LIII K channel Blockers and opener	IIIa: Non-selective K channel blockers	Ambasilide, amiodarone, dronedarone Dofetilide, ibutilide, sotalol Vernakalant Blocks K channels, ↓ repolarization, which leads to ↑ in AP duration and ERP ↓ re-entry Amio: Also ↓ SAN and AVN conduction	VT (w/o structural heart disease or remote MI), VF, AF with AV conduction via accessory pathways VF, PVCs Tachyarrhythmia associated with AF	HtoD, severe bradycardia, syncope without pacemaker, severe sinus node dysfunction, second and third degree AV block (unless with pacemaker) Cardiogenic shock. Prolonged QT Should not be used with class I or lll antiarrhythmics
	IIIb: Metabolically dependent K channel blockers	Nicorandil, penacidil ↓ AP recovery, refractoriness in all cardiac cells but for SAN	Nicorandil used for angina Penacidil: Under investigation for HTN	HtoD, cardiogenic shock, ↓ BP, atient at risk of MI, patients receiving soluble guanylate cyclase stimulators
	IIIc: Transmitter-dependent K channel blocker	Medication under review Prolongs APD and ERP, ↓RR	AF	
IV calcium handling modulators	IVa: Non-selective surface membrane ca channel blockers	Bepridil Verapamil and Diltiazem Blocks ca current, inhibits SAN pacing, AVN conduction, ↑ ERP and AP recovery time and PR interval Block L-type ca channels Most effective at SA and AVN ↓ HR and conduction	B: Angina pectoris and potential management of SVT SVT and VT (w/o structural heat disease), rate control of AF	HtoD. For verapamil: A-fib, A-flutter associated with WPW syndrome SSS, second and third degree AVB without pacemaker, HF with EF < 30%, hypotension HtoD. For diltiazem: All the above, newborns, acute MI with pulmonary congestion, administration within a few hours of IV β-blockers
	IVb: Intracellular ca channel blockers	Flecainide Propafenone Reduced SR ca	Catecholaminergic polymorphic VT	Flecainide: SSS, ↓ or ↑K, MI, second degree HB, RBBB

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Table 2 (continued)

Drug classification		Medication name and MOA	Indications	Contraindications
		release, reduced cytosolic and SR ca	PAF, A-flutter, PSVT	with left hemi B, chronic HF Propafenone: HF, cardiogenic shock, SSS (w/o pacer), bradycardia, BS
	IVc: Sarcoplasmic reticular ca, ATPase activators	Not clinically approved yet	Not determined yet	Note determined yet
	IVd: Surface membrane ion exchanger	Not clinically approved yet	Not determined yet	Not determined yet
	lVe: Phosphokinase and phosphorylase inhibitors	Not clinically approved yet	Not determined yet	Not determined yet
V: Mechanosensitive channel blockers	Transient receptor potential channel (TRPC3 and TRPC6) blockers	Under investigations: N-(P-amylcinnamoyl) anthranilic acid	Not determined yet	Not determined yet
VI Gap junction channel blockers	Cx (Cx40, Cx43, Cx45) blockers	Under investigations: Carbenoxolone	Not determined yet	Not determined yet
VII upstream target modulators	ACEI Electrophysiological and structural remodeling (fibrotic, hypertrophic, inflammatory)	Captopril, enalapril, delapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, cilazapril	HTN, heart failure and potential application reducing arrhythmic substrate	H to D, angioedema, bilateral renal artery stenosis, and prior deterioration of kidney function with ACE-I, hyperkalemia, pregnancy May also hold when BP $< 90/30$
	ARBs Electrophysiological and structural remodeling (fibrotic, hypertrophic or inflammatory)	Losartan, candesartan, eprosartan, telmisartan, irbesartan, olmesartan, valsartan	HTN, heart failure, and potential application reducing arrhythmic substrate	H to D, angioedema, bilateral renal artery stenosis, and prior deterioration of kidney function with ARBs, hyperkalemia, pregnancy
	Omega-3 fatty acids Electrophysiological and structural remodeling (fibrotic, hypertrophic, inflammatory)	Eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid	Post MI reduction of cardiac death, MI, stroke, and abnormal cardiac rhythm	HtoD, hypersensitivity to fish or shellfish, hepatic impairment May increase risk of bleeding
	Statins Electrophysiological and structural (fibrotic, inflammatory) remodeling	Atorvastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, pitavastatin, others	Post MI reduction of cardiac death, MI, stroke, and abnormal cardiac rhythm	Acute liver disease, pregnancy, lactation, elevation of liver enzymes, and conditions that increase AKI

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Table 2 (continued)

Drug classification	Medication name and MOA	Indications	Contraindications
II d	Digoxin Inhibits ca-K ATPase, causing ↑ chronotropic and ↓ionotropic effects	A-fib, A-flutter with RVR, HF	HtoD, VF ↓ dose by 30–50% when using amiodarone and 50% with dronedarone

Data on this table are from references [9–12]

Note: The reader is responsible for checking all drugs and verifying doses according to patient's age, liver/kidney functions, and comorbid conditions

AC, Acetyl choline; ACI, acetyl choline inhibitor; ACEI, angiotensin converting enzyme inhibitor; A-Fib, atrial fibrillation; AP, action potential; AKI, acute kidney injury action potential duration; Amio, amiodarone; ARB, angiotensin receptor blocker; ARI, adenosine receptor inhibitor; AV, atrioventricular; AVB, atrioventricular block; AVN, atrioventricular node; BP, blood pressure; β1S, β1 selective; BS, Brugada syndrome; CAD, coronary artery disease; ERP, effective refractory period; HB, heart block; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; HF, heart failure; HR, heart rate; HTN, hypertension; HtoD, hypersensitivity to drug or its components; IST, inappropriate sinus tachycardia; LV, left ventricular; MI, myocardial infarction, M2R, muscarinic receptor; MOA, mechanism of action; Nβ1S, non-β1 selective; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; RBBB, right bundle branch block; RR, repolarization reserve; SA, stable angina; SAN, sinoatrial node; SLE, systemic lupus erythematous; SR, sarcoplasmic reticulum; SSS, sick sinus syndrome; ST, sinus tachycardia; VA, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia; w/o, without ; WPW, Wolff-Parkinson-White

modulation by protein kinases are the target of new drug effects:

- Class IVa. They act on surface membranes of cells' Ca channel blockers.
- Class IVb. They act on intracellular Ca channel blockers.
- Class IVc. They act on sarcoplasmic reticulum Ca ATPase activators.
- Class IVd. They act on surface membrane ion exchange inhibitors.
- Class IVe. They act on phosphokinase and phosphorylase inhibitors cellular signals.

Class V. These drugs act on cation mechanosensitive ion channels and transient channels which suppress ectopic activity in hypertrophic cardiomyopathy. These drugs modulate the activity of channels in fibroblasts after cell death.

Class VI. These drugs act on connexins-associated channels. The initiation and propagation of AP is also affected by local currents through gap junctions, hemichannels, and cell-to-cell connections (connexin currents). Blocking gap junction currents can increase or reduce arrhythmias. These channels are important in remodeling process in the heart. Examples are carbenoxolone and peptide analog ZP-123.

Class VII. These drugs act on upstream modulatory targets. Fibrotic changes post-MI and chronic scarring in the heart lead to arrhythmias. This class includes drugs which inhibit remodeling and fibrosis. Examples are those who block the renin-angiotensin-aldosterone inhibitors, omega-3 fatty acids, and statins.

Ablation Therapy

Ablation therapy has gained a prominent role in the treatment of some tachyarrhythmias. Its aim is to deliver radiofrequency energy to destroy abnormal foci and pathways that cause the arrhythmia. The injury to heart tissue is thermal and creates scarring, inflammation, and then necrosis. Electrophysiology studies are used to identify, study, and accurately map the foci of arrhythmia. Indications for ablation therapy include WPW syndrome (usually curable), unifocal atrial tachycardia, AF, and idiopathic VT. Patients with VT may choose this as first-choice therapy. Ablation can be helpful in patients with structural heart disease, when drug therapy is not effective and when patients' ICDs have frequent discharge [4, 6–8, 13–15].

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Pacemakers and Defibrillators

Pacemakers and defibrillators are sophisticated computers which can pace, sense, and respond to arrhythmias by inhibiting and/or stimulating electrical activity in the atria, ventricles, or both. Pacemakers can also modulate their responses in a graded fashion. Patients at risk of life-threatening arrhythmias, or when arrhythmias severely compromise their cardiac function, must be referred to a cardiologist for evaluation of pacemaker and/or defibrillator placement. Several studies have demonstrated their effectiveness in preventing sudden death from arrhythmias [5–8].

The ACC/AHA and the North American Society of Pacing and Electrophysiology recommend the implantation of pacemakers in patients with complete third degree AV block; advanced second degree AVB (block of two or more consecutive P waves); symptomatic Mobitz I or Mobitz II AV block; second degree AV block with a widened QRS or chronic bi-fascicular block; and exercise-induced second or third degree AV block (in the absence of myocardial ischemia). They also recommend biventricular pacing for patients with dilated cardiomyopathy (ischemic and non-ischemic); those with an LVEF $<35\%$; those with QRS complexes >0.12 ms; and patients with New York Heart Failure class III or IV, despite optimal medical treatment [4–8].

Patients with implanted pacemakers need to be monitored regularly by cardiologist for proper function and programming, to check the battery life, and to monitor pacemaker activity and patient's clinical symptoms.

Defibrillators deliver unsynchronized electrical shocks to the heart with the aim to stop a lethal arrhythmia and re-establish a viable cardiac rhythm [15, 16]. There are several types of defibrillators: external, transvenous, implantable in the form of a cardioverter-defibrillator (ICD), or as part of a pacemaker. Some have become part of the general public domain, known as automated external defibrillators (AEDs), allowing even the lay public to use them successfully [16]. Today, most defibrillators deliver shocks in a biphasic truncated waveform which is more efficacious while using lower levels of energy to produce defibrillation. Defibrillation is only recommended for ventricular fibrillation and pulseless ventricular tachycardia.

Surgery

Two surgical therapies for atrial fibrillation are available: the obliteration of the left atrial appendage (LAA) and the Cox-Maze procedure, in which surgical disruption of abnormal conduction pathways within the atria is made.

LAA obliteration is a surgical procedure aimed at reducing the risk of thromboembolic events in patients with AF and possibly avoiding long-term anticoagulation. The rationale for obliteration is based on the observation that $>90\%$ of the thrombus forms in the LAA and is the main source of thromboembolism [3, 17–20]. Recently, the development of percutaneous procedures to obliterate the left atrial appendage has shown to be equal or superior to warfarin in reducing stroke and adverse cardiovascular events and all-cause mortality [16–20]. This approach should be considered when contraindication for long-term anticoagulation exists [3].

In the Maze procedure, incisions are made in the atria to isolate and interrupt re-entry circuits while maintaining the physiologic activation of the atria. The Maze procedure has undergone multiple revisions since its development, and it is considered for patients who need invasive cardiac surgery for other reasons [21].

Referral to Cardiologist

Cardiology referral is warranted when patients have complex cardiac disease, cannot tolerate the arrhythmia, need rhythm control, require ablation therapy, may benefit from surgical treatment, or need a pacemaker or defibrillator.

Supraventricular Tachyarrhythmias (SVT)

These arrhythmias originate above the ventricles and involve the atria, the AV node, or both for initiation and propagation. These are due to

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re-entry circuits or accessory pathways, most commonly the AV nodal re-entrant tachycardia, the atrioventricular re-entrant tachycardia, or the atrial tachycardia. In the absence of other conduction defects, the ECG shows a rapid HR with narrow QRS complexes. Wide QRS complexes indicate additional conduction abnormalities distal to AVN, such as bundle branch block and/or accessory pathways. These arrhythmias are treated as ventricular tachycardias.

In an acute setting, IV access and continuous cardiac monitoring are necessary. The first line of therapy is either IV adenosine or IV calcium channel blocker; they are both equally effective in terminating SVT. However, adenosine has quicker action, and it is short lasting. In patients with rare episodes and able to tolerate the episodes, a "pill on the pocket" (flecainide, diltiazem, or propranolol) is a reasonable choice. Patients with persistent or frequent episodes need continuous drug therapy, or they may benefit from radiofrequency ablation therapy which has high success rate in patients with AVN re-entry tachycardia [22].

When evaluating SVT, the following questions should be answered: "What is the ventricular response?", "Does it lead to a narrow or wide QRS?", "Is the arrhythmia regular or irregular?", and "What is the effect on cardiovascular status of the patient?"

Atrial Fibrillation (AF)

AF is the most common SVT seen in primary care. In addition to adverse effects on cardiac function, it increases the risk of stroke. AF has been identified as an independent risk factor for death [4, 22–26]. It worsens heart failure and increases mortality in the setting of myocardial infarct [22–26]. It causes about 10% of strokes, and these are more devastating and a major cause of disability [27–30]. Figure 2 shows the deleterious effect of AF [31].

AF results from uncoordinated atrial activation leading to deterioration of mechanical function. In the ECG, the normal P waves are lost, and irregular impulses reach the AV node and activate the ventricles at an irregular rapid rate, usually between 90 and 170 beats/min. The QRS complex remains narrow unless other conduction abnormalities coexist (Fig. 3). Enhanced automaticity of depolarizing foci and re-entry in one or more circuits are responsible.

AF may result from several disease processes with different prognoses and associated morbidities and mortalities. AF in patients younger than 60 with no underlying heart disease is known as lone AF and has good prognosis. AF due to congenital or acquired valvular disease carries the highest risk for stroke. Valvular vs non-valvular AF is defined by the presence or absence of

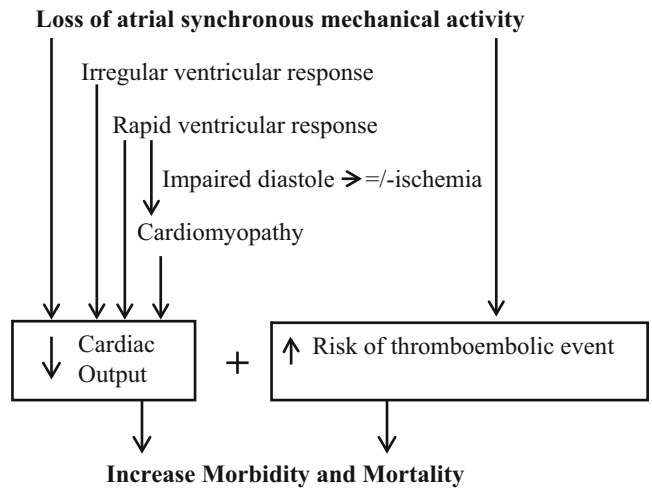


Fig. 2 Clinical implications of atrial fibrillation (Reproduced with permission from Atrial Fibrillation: Diagnosis and Treatment, January 1, 2011, Vol 83, No 1, issue of American Family Physician Copyright © 2011 American Academy of Family Physicians. All Rights Reserved.)

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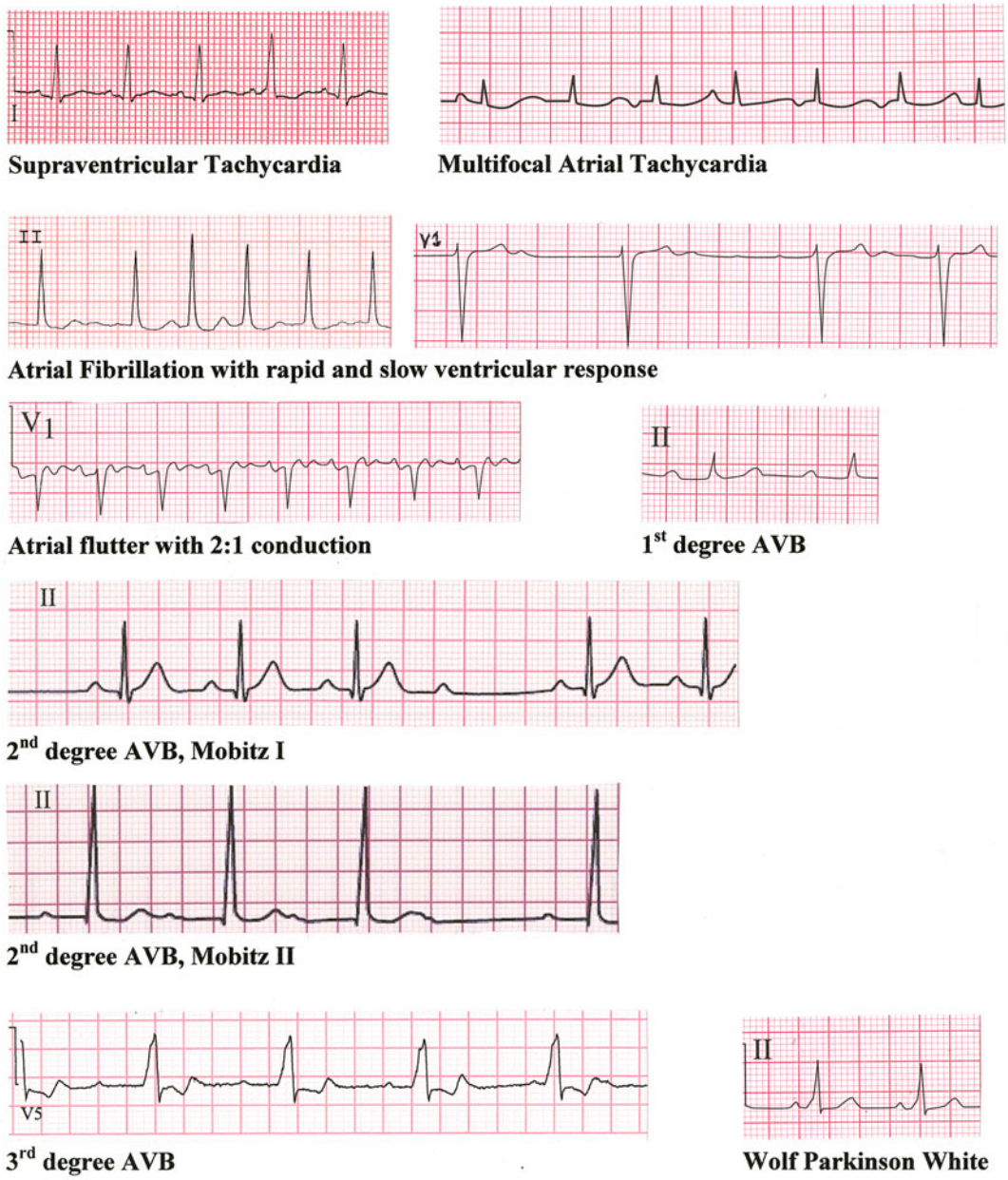


Fig. 3 Supraventricular Arrhythmias

moderate to severe mitral stenosis. Valvular AF that needs valve replacement requires long-term anticoagulation with warfarin [3]. AF due to non-cardiac disease such as hyperthyroidism or pulmonary disease is referred as secondary AF, and treating its cause resolves it. AF treatment and prognosis are affected by its duration and persistence. Paroxysmal AF is defined as episodes of self-resolving AF. Persistent AF lasts for >7 days and can still be terminated by cardioversion. Chronic AF is continuous and unresponsive to cardioversion. Paroxysmal and chronic AF carry the same risk for stroke. Persistent AF causes atrial remodeling (anatomical and physiologic changes)

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which leads to its perpetuation [3]. Patients with AF may be asymptomatic, have vague symptoms, or present with myocardial infarction, a stroke, or complete hemodynamic collapse. The diagnosis requires the typical ECG pattern: loss of P waves, narrow QRS complexes with a fast and irregular ventricular response. An event or Holter monitor may be needed to capture the arrhythmia.

The management of AF depends on the patient's clinical presentation. In cases of hemodynamic instability, stroke, or myocardial infraction, emergency evaluation and treatment is warranted, including emergency cardioversion.

The long-term treatment of AF poses three main therapeutic challenges: 1. Reverse to NSR by cardioversion or ablation; 2. control the ventricular rate and allow AF to continue; and 3. in either case, start anticoagulation.

Cardioversion can be achieved electrically or pharmacologically. Unless done emergently, or if AF is known to be less than 48 h, cardioversion requires 4 weeks pre- and 4 weeks post-anticoagulation. Pharmacologic cardioversion with antiarrhythmic drugs has limited efficacy. Commonly used drugs include flecainide (Tambocor), propafenone (Rythmol), dofetilide (Tikosyn), amiodarone (Cordarone, Nexterone, Pacerone), dronedarone (Multaq), and sotalol (Betapace, Sorine). Because they can trigger additional arrhythmias and have long-term adverse side effects, it is suggested to refer or co-manage patients with a cardiologist.

Ablation therapy is another way to restore NSR. It is gaining acceptance after the discovery of specific foci that trigger AF. These foci are at or near the pulmonary veins, the crista terminalis, and the coronary sinus [14, 28]. The ACC/AHA/HRS AF guidelines recommend it for patients with recurrent AF who are symptomatic but who have no structural heart disease [3, 4].

Most patients are treated with ventricular rate control vs rhythm control [3, 4, 28–30]. Rate control slows the ventricular response and improves diastolic ventricular filling, reduces myocardial oxygen demand, and improves coronary perfusion and mechanical function. β-blockers, metoprolol, esmolol, and propranolol, and non-dihydropyridine calcium channel blockers (CCB), diltiazem and verapamil, are used to achieve rate control with a goal of <80 during rest and <110 during exercise. More lenient rate control to a resting heart rate of <110 is reasonable in asymptomatic patients with normal left ventricular function. Digoxin is no longer a first or sole choice, but it can be used in addition to β-blockers or CCB [3]. Rhythm control is an option for patients in whom rate control cannot be achieved or who remain symptomatic.

Surgical treatments for AF include left atrial appendage obliteration and the Maze procedure. Both are invasive and are only considered in patients undergoing cardiac surgery for other reasons [17–21].

Anticoagulation

Although anticoagulation increases the risk for bleeding, it significantly reduces the risk of stroke and thromboembolic events, and therefore, it is an essential part of AF treatment. Several stratification tools to assess both the risk of stroke and the risk of bleeding have been developed. In spite of their limitations, they are useful in evaluating patients' risks and benefits for long-term anticoagulation.

The CHAD2DS2-VASc is an acronym that describes the main risk factors for stroke; it has been well established [32]. Table 3 shows the current risk stratification and recommendations for anticoagulation [3]. In general, anticoagulation is recommended for patients whose CHAD2DS2-VASc scores are >2 in males and for female patients >3. Similarly, the ATRIA and HAS-BLED are tools used to assess risk of bleeding [32–35]. Risk factors include anemia, severe renal disease, age, previous bleeding, hypertension, liver disease, labile INR, and drug or alcohol use.

Anticoagulation treatment has changed since the development of non-vitamin K antagonist drugs known as NOACs. Over decades warfarin (Coumadin, Jantoven) had been the cornerstone of anticoagulation therapy.

NOACs include direct thrombin inhibitor dabigatran and the newest factor Xa inhibitors rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa). All NOACs have been consistently shown to be non-inferior to/or superior to

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Table 3 CHAD2DS2-VASc stratification risk for stroke

CHA2DS2-VASc risk factor score	CHA2DS2-VASc total score	Adjusted stroke rate (percent/year)	Anticoagulation recommendation
Congestive heart failure/1 LV dysfunction	0	0	No
Hypertension 1	1	1.3	
Age < 65 0 65–75 1 > 75 2	2	2.2	Unless risk outweighs benefits, recommended options: Warfarin to target INR 2–3 Dabigatran 150 mg bid Rivaroxaban 20 md qd Apixaban 5 mg bid Edoxaban 60 mg qd For patients unable/or who refuse above choices: Aspirin 81 to 325 mg qd Clopidegel 75 md qd
Diabetes 1	3	3.2	
Stroke/TIA 2 Thromboembolism	4	4.0	
Vascular disease 1	5	6.7	
Female gender 1	6	9.8	
Maximum score 9	7	9.6	
	8	6.7	
	9	15.2	

Modified from the American Heart Association. http://circ.aha.journals.org/content/early/2014/04/10/CIR.0000000000000040.citation

warfarin in preventing stroke and systemic thromboembolism while having a safer profile, particularly in regard to intracranial bleeding [36–41]. The PROSPER study showed that in patients being treated for acute stroke, NOACs have better long-term outcomes relative to warfarin [40].

Due to warfarin's narrow therapeutic range, multiple drug and food interactions, need for frequent monitoring, and increase risk of bleeding, NOACs are recommended over warfarin in patients who have non-valvular AF, no mechanical valve, and no contraindications.

Warfarin is still the choice for patients who have moderate to severe mitral stenosis and mechanical valve. Many patients still take warfarin due to the higher cost of NOACs. The target goal is measured as the international normalized ratio (INR), and for most patients it is between 2 and 3 with non-valvular AF and an INR of 2.5–3.5 for those with valvular AF.

Warfarin is more effective than aspirin (Bayer Aspirin, Bufferin, Ecotrin) and clopidogrel (Plavix) alone or in combination, but it carries a higher risk for bleeding. It is estimated that warfarin lowers the risk of thromboembolic events by 68% while aspirin by 21% [42–46].

NOACs dosing needs to be adjusted for age, weight, kidney function, and liver disease. Table 4 shows a summary of approved anticoagulants available and their characteristics [36–41].

The main advantages of NOACs over warfarin include fixed dosing, no food interactions, fewer drug interactions, and no need for monitoring. Their major drawback is still high cost. Reversal therapy is now available for dabigatran and factor Xa inhibitors [47, 48]. The FDA has not approved them for valvular AF, pregnant, or lactating patients, and some are contraindicated in patients with advanced kidney disease.

Anticoagulation therapy must consider the patients' preferences. This requires a discussion regarding the risks, benefits, and a shared decision between physicians and patients.

Stopping anticoagulation due to emergencies and/or medical procedures may be necessary. The risk and benefits of doing so must be carefully assessed. Some data has shown worsening outcome when stopping anticoagulation [49]. If interruption is necessary, the recommendation is to bridge using unfractionated heparin or low molecular heparin [3, 4].

Atrial Flutter

Atrial flutter is an organized regular rhythm caused by a re-entry circuit around the tricuspid valve. It is often seen after cardiac surgery or cardiac ablation. AF and atrial flutter can occur

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Table 4 Pharmacological properties of approved anticoagulants available for the prevention of thromboembolism in non-valvular atrial fibrillation

Property Mechanism	Warfarin Vitamin K antagonist	Dabigatran Direct thrombin inhibitor	Rivaroxaban Factor Xa inhibitor	Apixaban Factor Xa inhibitor	Edoxaban Factor Xa inhibitor
Dosing	Variable (dose adjusted on basis of the international normalized ratio, INR INR goal is 2–3	150, 110 mg bid 75 bid if CrCl 15–30. Not recommended if CrCl <15	20 mg qd 15 mg if CrCl 15–50 Not recommended if Cr cl < 15	5 mg bid 2.5 mg bid for patients with 2 or more of the following: Cr > 1.5; age > 80y; weight < 60 kg CrCl <15, not defined	30–60 mg qd Avoid if Cr is >95 or < 30 Caution child-Pugh class B or C hepatic impairment
Oral bioavailability	100%	3–7%	60%	58%	64%
Time to effect (hr)	72–96	1–2	2–4	3–4	1–2
Half-life (hr)	40	12–17	5–9	8–15	10–14
Multiple drug and food interactions		Strong P-glycoprotein inducers			Minimal CYP450:3A4 substrate
		Strong P-glycoprotein inhibitors with concomitant kidney dysfunction	Strong P-glycoprotein inhibitors, strong cytochrome P450 inducers and inhibitors		

Cr, creatinine; CrCl, creatinine clearance; hr, hour
Modified from the American Heart Association. http://circ.aha.journals.org/content/early/2014/10/CIR0000000000000040.citation

back and forth and sometimes coexist, but they are different. In atrial flutter waves of depolarization activate the atria to contract regularly at about 280–300 times per minute, and if there are a healthy AVN and no AV node-blocking drugs, there is a 2:1 conduction resulting in a ventricular rate of about 150 beats per minute (Fig. 3). The preferred treatment for atrial flutter is ablation. AV node suppression drugs often change atrial flutter to AF, which may be better tolerated by patients. In the setting of cardiovascular compromise, electrical cardioversion may be necessary using biphasic defibrillator starting at 50 J energy shock.

Atrial or Sinus Tachycardia

Sinus tachycardia (Fig. 3) is in most cases a normal response of the heart to physiologic stressors such hyperthyroidism, dehydration, anemia, hypoxia, etc. A rare type of atrial tachycardia, called inappropriate sinus tachycardia (IST), is diagnosed when all possible causes have been excluded.

Frequent or Premature Atrial Contractions (PACs)

These are not classified as SVT. They generate from a single focus tachycardia but 1:1 P/QRS ratio with a single P wave morphology. When more than one focus triggers the arrhythmia, this is referred as multifocal atrial tachyarrhythmia (MAT). In this case the heart rate is greater than 100 beats/min, and the EKG has at least three different P wave morphologies with variable PP, PR, and RR intervals (Fig. 3). MAT is seen in heart disease, pulmonary disease, hypokalemia, and hypomagnesemia. When patients have different P wave morphologies and heart rate is <100 beats/min, the condition is referred as wandering pacemaker. Therapy is mostly focused at reversing potential causes, and CCB and BB are used to slow heart rate.

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Wolff-Parkinson-White (WPW) Syndrome

It occurs when one or more accessory pathways exist bypassing the AVN, allowing the ventricles to activate earlier than normal and resulting in tachyarrhythmia. The ECG shows a short PR interval with a slurring of the initial part of the QRS, making it wider, which is known as "delta wave" and represents pre-excitation (Fig. 3). Ablation therapy is curative and recommended. Drugs with AV node suppression effect such as BB, CCB, digoxin, and adenosine are contraindicated [5, 7].

Atrioventricular Arrhythmias

Atrioventricular block (AVB) results from an abnormal delay or interruption in the conduction of AP from the atria to the ventricles. This block can occur in the atria and at AVN and the His-Purkinje fibers, and it can be intermittent, complete or incomplete, and uni-fascicular, bi-fascicular, or tri-fascicular depending on the location of the lesion. The severity is described in degrees.

In first degree AVB, the delay conduction is at the AVN, but each AP from the SA reaches the ventricles. The ECC shows a prolonged PR interval, >0.2 s (Fig. 3). Usually this block does not cause significant symptoms, and it does not require treatment. Drugs with nodal suppression effects such as digoxin, verapamil, diltiazem, and beta blockers can be the culprit.

There are two types of second degree AVB, known as Mobitz I and II. Mobitz I occurs when the PR intervals progressively increase in length until a QRS is dropped. This phenomenon is also known as Wenckebach (Fig. 3). In Mobitz II, the PR interval remains constant, but not all APs from the SA are transmitted to the ventricles. Thus, the 1:1 P/QRS ratio is lost, and 2:1 or 3:1 conduction pattern appears. In patients with bi-fascicular block, a pacemaker is recommended.

In third degree AVB, there is complete blockage of conduction between the SA and AV nodes, and the atria and ventricles contract at different rates (Fig. 3). Depending on the ventricular response, the rate may be too slow to sustain appropriate circulation, and in some cases, it can lead to complete heart block. Most patients are symptomatic and require a permanent pacemaker.

Sick Sinus Syndrome (SSS) Also Known as Sinus Node Dysfunction (SND)

SSS describes a bradyarrhythmia caused by a sick SA node unable to be pacemaker, usually as a result of aging or heart disease. The SA node generates AP at a very slow rate leading to severe bradycardia, sinus pauses, and sometimes arrest. As the heart is unable to maintain adequate perfusion, patients experience lightheadedness, pre-syncope, syncope, dyspnea, and angina. Some patients develop brady-tachy syndrome with paroxysmal atrial tachycardia (most commonly AF) in response to the bradycardia. It is crucial to establish a correlation between the arrhythmia and symptoms to make the diagnosis of SSS, and a Holter or an event monitor is required. Treatment is focused at treating reversible causes, such as stopping drugs that suppressed the SA node, correcting electrolyte imbalances and hypoxia. Drug therapy has not been successful, and most patients require the implantation of a pacemaker [5, 7]. Patients with asymptomatic bradycardia do not need treatment but need close follow-up.

Ventricular Arrhythmias (VA)

VA are caused by electrical activation of ventricular cardiac cells without atrial or nodal influences, most commonly triggered by re-entry mechanism. Their characteristic ECG pattern shows wide QRS complexes (>120 ms), bizarre shape, no preceding P wave, and large T wave usually of opposite polarity to the QRS complex. They are serious arrhythmias associated with sudden cardiac death especially among patients with underlying cardiac disease and require cardiology referral. VA are classified according to their frequency, persistence, and effect on ventricular contraction [50].

Premature Ventricular Contractions, PVCs

PVCs show a wide QRS, no preceding P wave, and T wave is large and opposite to the QRS, giving a bizarre appearance (Fig. 4). They may

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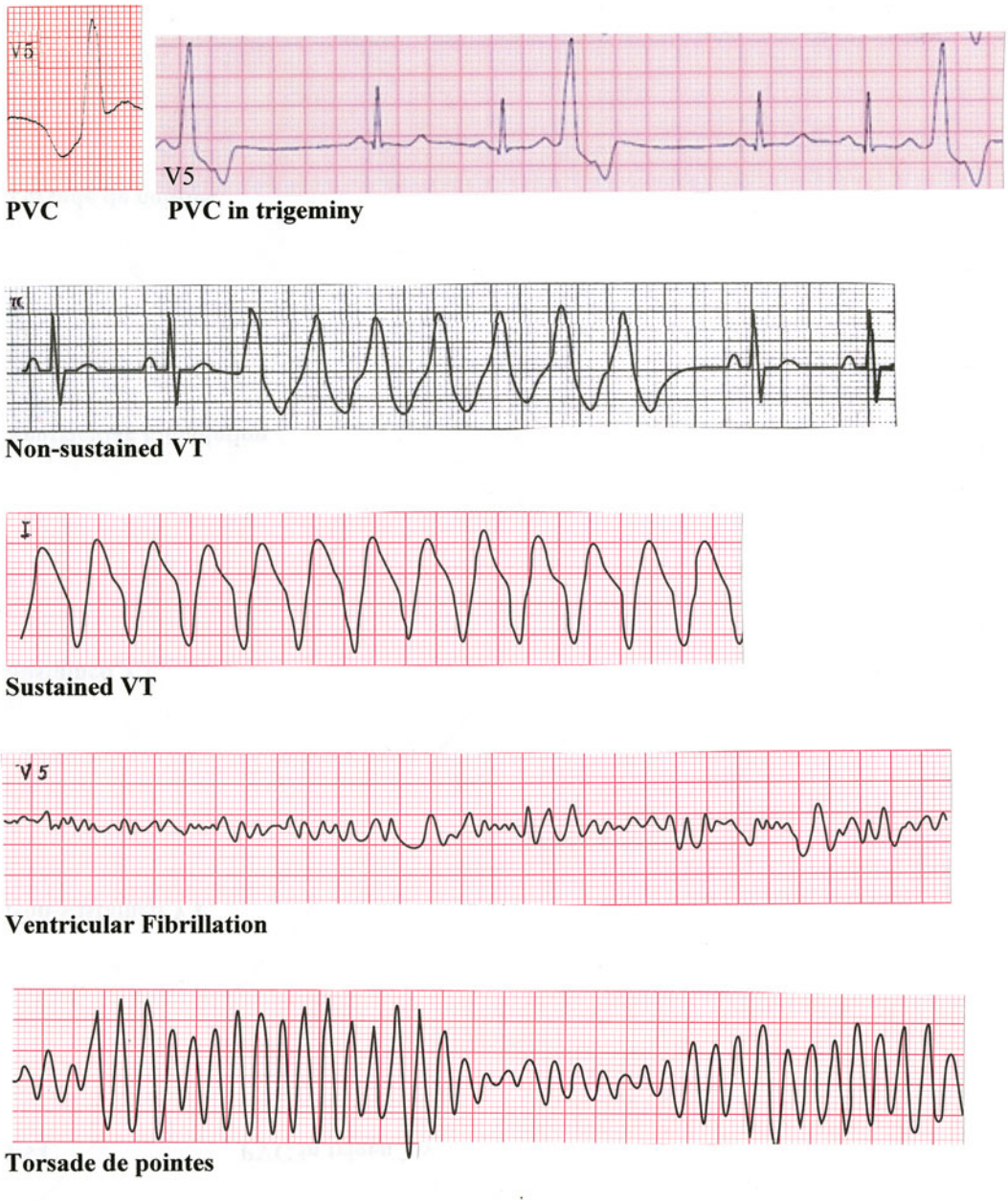


Fig. 4 Ventricular Arrhythmias

be triggered by electrolyte abnormalities (particularly hypokalemia, hypomagnesemia, and hypercalcemia), certain drugs, and stimulants. In addition to check electrolytes, magnesium and calcium, EKG, echocardiogram, a 24 h. Holter monitor is needed to assess their frequency, morphology, and effect on cardiac function.

PVCs are very common in the general population, and isolated events in patients with healthy hearts do not require treatment. However, in the

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setting of MI, ischemia, HF, and structural heart disease, they warrant immediate cardiology referral. First-line therapy for symptomatic patients is either a β-blocker, or non-dihydropyridine CCB, or antiarrhythmic drugs. Some patients may benefit from electrophysiology study (EPS) and catheter ablation if specific foci are identified. PVCs also can present in bigeminy, trigeminy, or quadrigeminy patterns when followed by one, two, or three normal beats, respectively (Fig. 4). Their clinical significance depends on their frequency, morphology, complexity, and patient's hemodynamic response.

Ventricular Tachycardia (VT)

It is defined as more than 3 PVCs in a row and HR > 100 beats/ min. VT is further characterized by duration and morphology [50]. Non-sustained VT lasts for <30 s. Sustained VT lasts >30 s, is symptomatic, and causes hemodynamic instability. VT may have single morphology (single focus), or may be polymorphic (two or more foci). Polymorphic rhythms are seen in patients with structural and ischemic heart disease, and they are associated with worse prognosis. It is key not to confuse VT with SVT associated with BBB or aberrant conduction since treatment is different.

Sustained VT requires emergent cardioversion and eventual ICD placement. Unstable polymorphic rhythms require defibrillation. Antiarrhythmic drugs (procainamide, amiodarone, and, less commonly, lidocaine) can be given to patients with monomorphic, stable, sustained VT, or when VT is refractory to cardioversion. Transvenous pacing may be necessary until a permanent ICD is placed. Patients with VT and ischemic heart disease benefit from β-blockers, ACEI or ARB, and aggressive treatment of HF. Class I antiarrhythmic agents are contraindicated post-MI and in HF. Patients with syncope should have EPS and ablation therapy if indicated.

Ventricular Fibrillation (VF)

This is life-threatening arrhythmia caused by the activation of multiple foci in the ventricles leading to loss of effective ventricular contraction. The EKG shows chaotic rapid polymorphic QRS complexes (Fig. 4). It requires immediate cardiopulmonary resuscitation and emergent defibrillation. VF is a common cause of cardiac arrest, and the use of automatic external defibrillators in the community is aimed to increase the chances of survival while activating the emergency response system. The most common cause of VF is severe CAD, history of MI, ischemia, and scarring. Patients with dilated cardiomyopathy have high mortality. More rare causes include genetic mutations. Long-term treatment of VF include revascularization, beta blockers, and ICD placement [5, 16, 51, 52].

QT Interval Prolongation

The QT interval in the EKG represents the time from the initial depolarization of the ventricles to their full repolarization. Prolongation of this interval can lead to deadly polymorphic ventricular arrhythmias and sudden death, such as torsades de pointes.

The QT interval varies with heart rate and it is necessary to correct for this. A corrected QT interval (QTc) also varies according to gender, for males 470 ms and for females 480 ms.

Hundreds of genetic mutations in K^+ channels which can cause QT prolongation have been identified. Recent progress in electrophysiology and genetic testing helps to identify and stratify patient's risk for these arrhythmias [53].

In addition to antiarrhythmic drugs, there are commonly used drugs in primary care, which can also prolong QT interval. Some examples include macrolide and fluoroquinolones antibiotics, some antihistamines, methadone, antipsychotic, and others.

Therefore, it is important for physicians to be aware of drugs that can prolong QT interval, their potential additive effects, and magnifying effect in the setting on hypokalemia and hypomagnesemia and any condition that causes hypoxia [54].

Torsades de Pointes

It is a rare form of VT characterized by repeated cycles of QRS complex changing in amplitude

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and twisting along the isoelectric axis, giving a unique pattern in the ECG (Fig. 4). It is associated with a significant QT prolongation, >600 ms. Although torsades can self-terminate, it can also degenerate into VF. Treatment requires IV magnesium given under continuous cardiac monitoring (even when Mg is normal). Temporary transvenous pacing can be used, with atrial pacing preferred to maintain the atrial filling, except in patients with AVB where ventricular pacing is best. Long-term therapy includes β-blockers (except in congenital torsades) and permanent pacing. In refractory cases an ICD is necessary, and rarely, thoracic sympathectomy is done.

VF and torsades are associated with sudden cardiac death. Since most events occur outside the hospital, recognition by lay persons, activation of the emergency system, immediate CPR, and defibrillation when indicated are key to survival [16, 51]. This has been the reason to install automatic external defibrillators (AEDs) in public places [51].

Summary

Arrhythmias are commonly seen by family physicians in the office. Immediate recognition of arrhythmias causing cardiovascular instability is key to improving patients' survival, sometimes requiring activation of the emergency system. Full evaluation, diagnosis, and treatment are warranted for all patients presenting with an arrhythmia or with suggestive symptoms, despite normal exams and/or EKGs. Reversible causes should be treated as well as comorbidities. Treatment option is tailored to the type of arrhythmia and must reflect a shared decision-making between patients and doctors, based on best available evidence and the patients' preferences.

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Valvular Heart Disease

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Sophia Malary Carter, Wendy Bocaille, and Santos Reyes-Alonso

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Introduction

Valvular heart disease occurs when one or multiple valves of the heart are damaged or diseased. About 2.5% of the US population has valvular heart disease, but it is more common in older adults. About 13% of people born before 1943 have valvular heart disease [1]. In 2017, there were 3046 deaths due to rheumatic valvular heart disease and 24,811 deaths due to non-rheumatic valvular heart disease in the USA. Nearly 25,000 deaths in the USA each year are due to heart valve disease from causes other than rheumatic disease. Valvular heart disease deaths are more commonly due to aortic valve disease [2]. There are several causes of valvular heart disease, including congenital conditions, infections, degenerative conditions (wearing out with age), and conditions linked to other types of heart disease [1]. Valvular heart disease is recognized by finding a heart murmur. Here, even more than elsewhere in cardiology, the physical findings are all important to making a diagnosis and assessing severity. Often, they trump the results of special testing. Murmurs may first be detected in a symptomless patient, perhaps a young would-be athlete at a high school physical examination, or they may be the clue in someone with dyspnea and fluid retention that valvular disease is the reason for their cardiac failure [3]. The family physician is in a particularly challenging position because we will be addressing these potential concerns at every stage of life and often may be dealing with determining the significance of a new heart sound as an incidental finding. Valvular disease may lead to decreased functional status, permanent structural changes, and increased mortality. Timely diagnosis and appropriate testing and consultation are the goals of the family physician, in order to prevent the negative sequelae of inappropriately addressing valvular disease. Learning maneuvers and understanding the sounds present within the heart facilitate appropriate diagnosis [4].

The Third Heart Sound

The third heart sound (S3) is the most difficult heart sound to identify on auscultation. S3 occurs in early diastole (during passive filling) when the ventricle is dilated and noncompliant. It will be heard after

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S2, with low frequency. Its significance varies depending on to the age of the patient. It can be interpreted as physiologic in patients under 30 years old with no structural or functional cardiac condition (thyrotoxicosis, pregnancy, and anemia). It is suspicious in patients between 30 and 40 years of age and it is considered pathologic in patients older than 40 years old often correlating with dysfunction or volume overload what is seen in patients suffering from pregnancy, thyrotoxicosis, valvular regurgitations, and excessive fluid overload. Right ventricle S3 is best heard (sometimes only) during inspiration because negative intrathoracic pressure increases RV filling with the patient supine. Left ventricle S3 is then best heard during expiration with patient in left lateral decubitus position [5–7].

The Fourth Heart Sound

The fourth heart sound (S4) is produced by augmented ventricular filling, caused by atrial contraction, near the end of diastole. It is auscultated immediately prior to S1 and it is a result of decreased compliance within the ventricles. S4 is similar to S3 and is best heard with the bell of the stethoscope. During inspiration, RV S4 increases while LV S4 becomes less intense. S4 is typically associated with hypertrophy of the ventricles. The fourth heart sound is best heard at the level of the apex and can be also palpable. In general it is accepted that the presence of S4 is highly associated with pathology although there is some disagreement in regards of the presence of audible S4 in absence of cardiac pathology [7, 8].

Physical Exam and Diagnostic Approach

Auscultating heart murmur can be difficult sometimes. In general physicians must exam the patient in a quiet room minimizing external surrounding noises in order to be able to fully characterize the murmur. First step when examining a murmur is to determine relation with the cardiac cycle since all diastolic murmurs must be considered pathologic until proven otherwise. The second step would be grading the murmur. There are several approaches to determine the grade of the murmur. In general every murmur whose intensity is louder than S1-S2 should be considered Grade III or greater and requires further evaluation with echocardiogram. Grade VI can be heard even without the stethoscope. Grade V can be auscultated with the stethoscope half off the chest wall. Grade IV, V, and VI have associated thrill.

Classification of cardiac murmurs (six):

- **Grade I:** Audible under optimal conditions by an expert.
- **Grade II:** Easy to hear with stethoscope but soft.
- **Grade III:** Moderately loud, no thrill.
- **Grade IV**: Very loud with a palpable thrill, with stethoscope on chest.
- **Grade V:** Audible with stethoscope partly off chest with a thrill.
- **Grade VI:** Audible without a stethoscope with a thrill.

Most of the murmurs foundin children and adults are benign innocent murmurs in adults [8]. In general and for practice purposes further workup is warranted in patients with systolic murmurs Grade III or more and in every patient with a diastolic murmur. In such cases an echocardiogram should be ordered as the best initial step.

Physical Maneuvers

Exam room maneuvers may alter the qualities of a murmur and may help to define and diagnose innocent versus pathological murmurs. Maneuvers that increase afterload are better for ruling out murmurs than ruling in. Methods of increased peripheral resistance, such as the patient gripping something hard, decreases outflow from the heart and thus decreases outflow, physiologic, and innocent murmur volumes. Decreased preload maneuvers decrease venous return to the heart, so murmurs affected by filling, including innocent and physiologic murmurs and outflow, mitral valve, and tricuspid valve murmurs, will all have a decrease in audible volume.

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Decreasing preload is done best by Valsalva maneuvers. A Valsalva maneuver is executed by asking the patient to take a deep breath, hold it, and bear down like performing a bowel movement.

Increased preload maneuvers increase venous return and filling of the heart. Squatting position is the easiest method to increase preload. Though maybe variable, most outflow murmurs increase in volume when a patient is squatting, and murmurs caused by hypertrophic cardiomyopathy (HCM) or mitral valve prolapse (MVP) decrease in volume [6, 8].

In other words, a larger volume of blood in the heart (increase preload through squatting and lift legs) will increase the audible volume of the murmur except in patients with mitral valve prolapse and hypertrophic cardiomyopathy. Less volume of blood in the heart (decrease preload through Valsalva maneuver) will cause the opposite effect.

Definitions of Severity of Valve Disease

It is important to access the severity of a valvular disease. This allows us to determine if valvular replacement is indicated. Valve replacement are reserved for patient with severe valvular disease. Severity is based on multiple criteria, including symptoms, valve anatomy, valve hemodynamics, and the effects of valve dysfunction on ventricular and vascular function. Indications for intervention and periodic monitoring are dependent on:

1. The presence or absence of symptoms
2. The severity of VHD
3. The response of the LV and/or RV to volume or pressure overload caused by VHD
4. The effects on the pulmonary or systemic circulation [6]

Stages of Valvular Heart Disease

Stage A: Patient with risk factors for developing VHD

Stage B: Patient with a progressive VHD and presence of mild to moderate severity and asymptomatic

Stage C: Patient with asymptomatic severe VHD

- C1: Patient with severe VHD, no symptoms with left/right ventricular function remains compensated
- C2: Patient with severe VHD, no symptoms with decompensated left/right ventricular function

Stage D: Patient with severe VHD who has developed symptoms already [9]

Key Points in Treatment

Treatment and management will be discussed in details under specific topics. In general, valvular diseases are treated either medically or with surgery. Considering that an increase in preload will worsen the severity of the murmur except in mitral valve prolapse and hypertrophic cardiomyopathy, medical management of almost all murmurs must focused on the reduction of the preload and decrease afterload. In MVP and HCM the goal is to improve the filling of the heart. This is achieved by the use of beta blockers (increase filling time/diastole) and avoiding dehydration or any condition that decrease circulating volume.

Aortic Regurgitation (AR)

Aortic regurgitation occurs when the aortic valve does not close tightly due to incompetence of the aortic causing flow from the aorta into the left ventricle during diastole. Causes include idiopathic valvular degeneration, rheumatic fever, endocarditis, myxomatous degeneration, congenital bicuspid aortic valve, syphilis, and connective tissue and rheumatologic disorders. Acute aortic regurgitation is an early diastolic murmur that is the result of the blood flowing retrograde into the left ventricle and has been described as a blowing decrescendo at the left sternal border best heard when patient has held breath after exhalation and is leaning forward [4, 7]. AR can be classified as acute or chronic depending on the onset of presentation. Acute aortic regurgitation derives from a rapid change in the aortic valve causing an acute abnormality, which may arise from etiologies

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including infective endocarditis or changes in the aorta such as aortic dissection. Acute aortic regurgitation is the result of life-threatening abnormalities, and early diagnosis with echocardiogram or CT imaging is crucial to facilitate rapid surgical intervention [4].

Chronic aortic regurgitation is also a diastolic murmur, and as with all diastolic murmurs, a referral to a cardiologist should be considered for echocardiography and further recommendations [4].

Etiology

Acute aortic regurgitation (AR) may result from abnormalities of the valve, most often endocarditis, or abnormalities of the aorta, primarily aortic dissection. Acute AR may also occur as an iatrogenic complication of a transcatheter procedure or after blunt chest trauma. The acute volume overload on the LV usually results in severe pulmonary congestion, as well as a low forward cardiac output. Urgent diagnosis and rapid intervention are lifesaving [9].

Chronic AR has a wide variety of causes that requires early identification before determining treatment options. Causes can be divided in three groups including conditions that involves the valve itself, the aorta, and diseases affecting both the valve and the aorta [3].

Diseases of the Valve

- Bicuspid aortic valve
- Following endocarditis
- Rheumatic valve disease

Diseases of the Aorta

- Connective tissue disorders
- Marfan syndrome
- Familial aortic ectasia
- Other rare, inherited vascular disorders
- Aortic dissection
- Inflammatory disorders
- Vasculitis (Takayasu disease)
- Giant-cell arteritis
- Syphilis

Diseases Affecting Aorta and Valve

- Spondyloarthropathies
- Ankylosing spondylitis
- Reiter syndrome
- Psoriatic arthropathy

Symptoms and Physical Findings

Acute AR causes symptoms of HF and cardiogenic shock. Patient will present with dyspnea on exertion that can progress to dyspnea at rest, orthopnea, and paroxysmal nocturnal dyspnea (PND), with physical findings typical of left side heart failure such us bilateral symmetric and progressively ascending crackles, associated with tachycardia, hypotension, JVD, and other signs consistent with cardiogenic shock [7].

Chronic AR is typically asymptomatic for years with signs and symptoms of HF developing insidiously. Symptoms associated with chronic aortic regurgitation include syncope, angina, and reduced exercise tolerance. As the disease progresses and left ventricular function begins to decrease, symptoms associated with systolic heart failure may arise including lower extremity edema and increasing dyspnea [4, 7].

The findings on physical examination in patients with chronic AR are primarily related to the increased stroke volume and widened pulse pressure. The peripheral pulses demonstrate an abrupt rise of the upstroke and a quick collapse (water hammer or Corrigan pulse). Apical impulse is hyper-dynamic lateralized to the left and inferiorly. Depending on severity is possible to auscultate a thrill usually over the base of the heart but also can be heard over the carotids and suprasternal notch. The classic murmur of AR is a high-frequency, blowing, and decrescendo diastolic murmur, usually heard in the aortic area but also audible in the left third and fourth intercostal spaces along the sternal border. Initial phases of the disease murmur are mild and present

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only during early diastole but with progression it starts becoming more like a holodiastolic murmur. AR murmur will increase in intensity with increase preload or afterload maneuvers and will feel less intense with maneuvers that decrease blood pressure, such as standing, amyl nitrate inhalation, or the strain phase of the Valsalva maneuver [10].

Most common signs seen in patients with chronic AR are summarized below [3].

Quincke's sign: Nail bed pulsation
Corrigan's pulse: Visible carotid pulsation
de Musset's sign: Head bobbing to pulse
Müller's sign: Uvula bobbing to pulse
Duroziez's sign: Diastolic bruit with compression of the femoral artery at the groin
Hill's sign: Systolic pressure in the leg >10 mmHg higher than measures at the brachial artery
Traube's sign: Pistol-shot sounds best heard over the femoral artery

Diagnosis of Aortic Regurgitation

The initial diagnosis of any suspected valvular disease is with a transthoracic echocardiogram (TTE) which is the best tool to assess valve anatomy and etiology, concurrent valve disease, and associated abnormalities, such as aortic dilation. Doppler echocardiography provides accurate noninvasive determination of valve hemodynamics. For regurgitant lesions, calculation of regurgitant orifice area, volume, and fraction is performed, when possible in the context of a multiparameter severity grade based on color Doppler imaging, continuous- and pulsed-wave Doppler recordings, and the presence or absence of distal flow reversals. Other more invasive procedures sometimes can be used in order to determine a final diagnosis and stratified severity of AR especially when noninvasive tests like TTE cannot provide accurate information or when there is no correlation between noninvasive imaging and clinical findings. In these cases cardiac catheterization should be considered and will provide valuable information that will help significantly in the decision-making process regarding surgical intervention. Exercise testing can be considered in patients which physician is not sure about the real physical limitations the patient is experiencing. Cardiac magnetic resonance imaging is another option for initial evaluation and further follow-up since it can provide highly accurate assessment of LV volumes, mass, and ejection fraction; it can also provide excellent visualization of the aortic root and ascending aorta.

Cardiac MRI can be used to obtain accurate information regarding regurgitant volumes and flow [9, 10].

Natural History, Complications, and Follow-Up

Aortic regurgitation is a chronic progressive condition which causes significant hemodynamic changes in the heart that leads to compensatory remodeling of the left ventricle over time with a subsequent decreased LV function and can eventually lead to severe HF. Once such remodeling is established the probability of full recovery even with appropriate treatment including valve replacement is minimal. With treatment, the 10 years survival for patients with mild to moderate AR is about 80–95%. With timely valve replacement before HF, long-term prognosis is good, however for those with severe AR and HF is really poor. That is why early diagnosis is important and adequate initial workup and follow-up of these patients in order to intervene in a timely manner [4]. Patients with AR requires appropriate clinical and echocardiographic follow-up. New guidelines have established a regular follow-up with transthoracic echocardiogram (TTE) depending on the severity of the disease. For patient with AR Stage B (Progressive) evaluation is needed with TTE every 3–5 years if mild severity symptoms are present. Patients with AR Stage B (Progressive) will be evaluated with TTE every 1–2 years if moderate severity symptoms are noticed. And for severe asymptomatic (Stage C1) patient will need TTE every 6–12 months with the possibility of more frequent evaluation if LV dilation is present [7, 9].

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Medical Therapy and Timing for Surgery

Treatment for acute AR is aortic valve replacement plus treating any underlined medical conditions that led to the AR. Treatment for chronic AR varies depending on symptoms and the degree of LV dysfunction. Patient experiencing symptoms during an exercise testing will require valve replacement before developing signs and symptoms of HF [8]. For asymptomatic patient with chronic AR (Stages B-C), treatment for HTN is recommended when BP is >140/90 (level B recommendation). In patients with severe AR with symptoms and/or LV systolic dysfunction (Stages C2 and D) but prohibited surgical risk guideline–directed medical management (GDMT) for LVEF with ACEI, ARBs and sacubitril-valsartan (Entresto) are recommended (also level B recommendation) [9].

Valve replacement is the goal for treatment of chronic AR. Most recent recommendations are summarized below:

- Surgery is recommended for patients that are symptomatic regardless of LV function
- Asymptomatic patient with LVEF <=55%
- Patients with moderate/severe AR that are undergoing cardiac surgery for other reasons
- Asymptomatic patients with LVEF >55% but left ventricular end systolic diameter >50 mm on echocardiogram, surgery can be considered
- Asymptomatic patients with severe AR and normal LVEF >55%, but with declining EF in at least three serial studies, or if progressive increase LV dilation into the severe range (>65 mm end diastolic dimensions LVEDD) [9]

Aortic Stenosis

Aortic stenosis (AS) is narrowing of the valve orifice obstructing blood flow from the left ventricle to the ascending aorta during systole. Causes include congenital valve disease (unicuspid and bicuspid valve), degenerative sclerosis, and rheumatic disease. Progressive untreated AS will result in a classic triad of syncope, angina, and exertional dyspnea. Eventually heart failure and arrhythmia may develop. A carotid pulse with small amplitude and crescendo-decrescendo ejection murmur are typical of the disease. Diagnosis is based on physical findings and echocardiography. Asymptomatic patient will not require treatment while symptomatic cases can be treated with balloon valvulotomy (especially in children) and valve replacement more commonly used in adults [7].

Etiology

Aortic stenosis (AS) etiologies are diverse. Causes can be divided for practical purposes in congenital and degenerative calcific disease. Congenital causes are unicuspid aortic valve, usually severe and presents in children, and congenital bicuspid aortic valve with a murmur that can be present since childhood and it is recognized as the most common cause of AS as well as AR. AS secondary to bicuspid aortic valve develops in middle age with associated valve calcification.

Degenerative calcific AS develops usually later in life (late middle age) and it is not associated with any congenital anatomic defect (trileaflet aortic valve). The earliest manifestation is the aortic sclerosis characterized as thickening of the leaflets, with the presence of heart murmur, and a gradient less than 25 mmHg. Progression of this sclerosis is pathologically similar to that of atherosclerosis and it is linked to the same risk factors [11–13].

Another significant cause of AS is rheumatic disease which tends to be much more common in developing countries where rheumatic fever is highly prevalent. Patients who have suffered rheumatic fever can have not only aortic valve disease but also mitral regurgitation/stenosis. Rheumatic valve disease is characterized by fusion of the commissures between the leaflets resulting in stenosis of the orifice which is histologically typical of rheumatic disease [14].

Symptoms and Physical Findings

Congenital AS is usually asymptomatic until around the ages between 10 and 20 years old

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when symptoms start to develop insidiously. Regardless of the etiology untreated AS ends up a classic triad that includes syncope, angina, and exertional dyspnea. Other clinical manifestations and physical findings are those related to heart failure and arrhythmia, when ventricular fibrillation can be potentially fatal. In general symptoms of AS are absent until AS is severe enough (valve area <1 cm^2, the jet velocity is over 4 m/sec, and/or the transvalvular gradient exceeds 40 mmHg).

Unlike AR there are no visible signs associated with AS. Carotid and other peripheral pulses are diminished and delayed on exam compared to LV contraction (pulsus parvus et tardus). LV impulse is displaced when signs and symptoms start to develop. A palpable fourth heart sound can be felt at the apex with a systolic thrill best felt at the level of the left upper sternal border present in severe cases only. Systolic blood pressure is elevated in mild and moderate cases with a drop when AS becomes severe.

The classic sign on auscultation is a crescendo-decrescendo ejection murmur best heard with the stethoscope placed at the left upper sternal border with the patient sitting and leaning forward. The intensity of the murmur is soft when obstruction is not severe and louder when progresses to a severe form of the disease, when the crescendo phase tends to longer and the decrescendo phase becomes shorter. Murmur is louder with maneuvers that increase left ventricular volume [7, 15].

Diagnosis of Aortic Stenosis

Diagnosis of AS is suspected by symptoms and physical exam and finally confirmed by echocardiography. Medical and interventional treatments rely on an accurate diagnosis and staging of the disease. As any other valvular disease staging is based on the presence of symptoms and hemodynamics identified on echocardiogram. Stage A are patients identified as at risk of having AS and includes patients with congenital aortic disease and aortic sclerosis. Stage B are patients with no symptoms with mild to moderate AS. And Stage D are considered patients with severe AS with the classic clinical manifestations.

Transthoracic echocardiogram (TTE) is the recommended test for an accurate diagnosis of the cause, hemodynamic assessment of the severity, and to determine LV size and systolic function in order to understand prognosis and timing for valve intervention, as well as other associated valvular diseases. Severity of AS can be misinterpreted in the presence of elevated uncontrolled hypertension and thus is recommended to reassess with TTE in such cases when BP is adequately controlled.

Dobutamine stress echocardiography is used to distinguish severe AS with LV systolic dysfunction and primary causes of myocardial dysfunction with less than severe AS.

Aortic valve calcification is a strong predictor of progression and clinical outcome. Calcium deposition can be determined by CT imaging. Agaston score threshold for severe AS in women is 1300 and 2000 in men. CT imaging also is used for procedural planning in patients undergoing TAVI, for measurement of annulus area, leaflet length, and the annular-to-coronary ostial distance.

Cardiac catheterization is used sometimes to determine if the presence of angina is secondary to coronary artery disease or when there is discordance between clinical findings and echocardiographic results. EKG and chest X rays can be useful and may show signs of LVH, axis deviations, electrical blocks, ST-T changes, cardiomegaly, and calcification of the aortic cusps. Exercise stress test can be useful in patients with AS that are asymptomatic and when the functional capacity of the patient is not clear. Exercise-induced angina, early dyspnea on exertion, dizziness, and syncope during test are considered symptoms of AS [7, 9].

Natural History, Complications, and Follow-Up

The natural progression of AS could be either slow or rapid and thus requires regular follow-up and evaluation especially in sedentary elderly patient in which functional status sometimes is unclear. Patients with mild disease are unlikely

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to develop symptoms due to AS over the course of 5 years. Untreated patient has a mean survival of 5 years after angina starts, 4 years after syncope, and 3 years after signs and symptoms of CHF appear. Progression has significant individual variability. Older patients are more likely to have rapid progression [7, 9, 15, 16]. For asymptomatic patients with severe AS the event-free survival rate is 56–63% at 2 years and 25–33% at 4 to 5 years [17].

Regular follow-up is very important considering that symptoms tend to progress insidiously and patients cannot recognized them clearly. Follow-up visits must include clinical and echocardiographic (TTE) assessments with the main goal of preventing severe irreversible diseases. Stage B patient with mild and moderate disease will require TTE every 3–5 years and 1–2 years, respectively. Stage C1 patient needs to be evaluated with TTE every 6–12 months. Patients classified in higher categories are candidates for interventions and need a different approach [9].

Medical Therapy and Timing for Surgery

Treatment of AS will depend on if the patient is asymptomatic or symptomatic. For asymptomatic patients regular clinical follow-up and TTE are indicated in order to identify early symptoms and signs of AS. Even when there is no medical therapies that have proven to delay the progression it is still recommended a conventional CVD risk assessment and treatment based on guidelines considering that some studies have shown that valve calcification and progression are increased in patients with LDL cholesterol >130 [6, 15, 18]. Patients with associated hypertension must be adequately controlled with close monitoring and careful titration of the medications to avoid hypotension. Hypertensive patients with more severe AS requires a greater degree of caution when treated. There are no studies studying the use of specific antihypertensive medications, although it is known that diuretics decrease the stroke volume and thus should be avoided in AS patients. ACE inhibitors may be beneficial preventing LV fibrosis, in addition to control of hypertension [6, 17, 19]. Patients requiring medical management must be treated with ACE inhibitors, ARBs, and beta blockers in order to optimize left ventricular systolic dysfunction [4]. Nitrates are contraindicated because of its effects lowering preload. Patients with AS may require antibiotic prophylaxis prior to dental work and other potentially contaminated procedures [3].

Aortic valve replacement (AVR) is the definitive treatment for AS. All symptomatic patients thought to be secondary to AS are candidates for AVR. Asymptomatic patients with severe AS with or without LVEF <50% are also accepted as candidates for AVR. Other clinical scenarios must be evaluated more carefully before recommended surgical intervention [9].

Hypertrophic Obstructive Cardiomyopathy

Etiology

Hypertrophic obstructive cardiomyopathy (HOCM) is a heart condition that arises from genetic mutations in multiple sarcomere genes. These genes are responsible for the proper structural integrity of protein that makes up the contractile apparatus of the heart. There is an incidence of 1 in every 500 individuals worldwide, with an estimated 1% annual mortality rate [20]. It is among the most common causes of sudden cardiac death in young athletes in the USA. Hypertrophic cardiomyopathy is inherited in an autosomal dominant pattern. However, there is varying penetrance depending on the genetic mutation involved [21].

Signs and Symptoms

Individuals tend to have a thickened interventricular septum of the heart leading to left ventricular outflow obstruction. While some patients may be asymptomatic, others present with symptoms due to this outflow obstruction,

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especially with exertion. This may include chest pain, dyspnea, palpitations, malaise, presyncope, or exertional syncope due to cardiogenic shock. Cardiogenic shock in such patients may not always present with autonomic prodromal symptoms as in the case of other benign syncopal etiologies. Syncope due to cardiogenic shock tends to resolve once cardiac output is restored [22].

Physical Findings

There are no clear specific findings for HOCM, but there are those that would prompt further evaluation leading to this diagnosis. On examination, a systolic ejection murmur can be heard on auscultation. There are different maneuvers that change the intensity of the murmur. Standing and Valsalva strain phase causes decreased venous return to the heart, resulting in decreased left ventricular cardiac output. The left ventricular outflow track is narrowed, and can be exacerbated by anterior motion of the mitral valve leaflets. This then increases the intensity of the murmur. Squatting, handgrip, or supine leg raise, however, causes increased venous return. This volume increases the left ventricular outflow tract and lessens obstruction by systolic anterior motion of the mitral valve. As a result, squatting, handgrip, or supine decreases the intensity of the murmur. Some nonspecific findings for individuals with HOCM include voltage changes as seen on EKG, confirming left ventricular hypertrophy. Echocardiogram and cardiac MRI are specific and diagnostic. Chest X-Ray may reveal left atrial enlargement due to mitral regurgitation [23].

Natural History and Complications

Medical Therapy and Timing of Surgery

Some patients may be hypotensive in response to exercise, or have episodes of ventricular tachycardia resulting in cardiogenic shock and syncope. Complications include sudden cardiac death. There are those that develop heart failure or atrial fibrillation as a sequela of left ventricular dysfunction.

Individuals diagnosed with hypertrophy obstructive cardiomyopathy are to avoid high-intensity physical activity that could further exacerbate cardiac outflow. Patients that are clinically stable can be actively monitored with echocardiogram every one to two years. Those with left ventricular outflow tract obstruction can be managed with non-vasodilating beta blockers as first-line therapy. Non-dihydropyridine calcium channel blockers, including Verapamil and Diltiazem, are second-line agents for those that are unable to tolerate beta blockers. Individuals that develop atrial fibrillation or heart failure as a sequela of poor left ventricular function can be managed by using respective agents for atrial fibrillation and heart failure. In the setting of atrial fibrillation, anticoagulation therapy is indicated irrespective of CHA2DS2-VASc score. Other more invasive measures such as implantable defibrillators may be indicated for those with increased risk of sudden cardiac death. Those increased risks include prior history of cardiac arrest, a family history of sudden cardiac death, ventricular tachycardia, or recurrent exertional syncope [24].

Mitral Stenosis

Etiology

The most common cause of mitral stenosis is rheumatic heart disease. Rheumatic mitral stenosis is commonly seen in developing countries more so than developed countries. If seen in developed countries such as the USA, the outbreak tends to arise from increased virulence of streptococcal strain or from someone that is from an area with high prevalence of the disease. Rheumatic mitral stenosis is caused by cross-reactivity of the streptococcal antigen and the valvular tissue, and not due to an infectious process on the valve. This cross-reactivity causes an inflammatory process to occur that damages the mitral valve. Calcifications of the mitral valve leaflets, fusion of the leaflet commissures, and fibrotic changes to the chordae tendinae can occur. The severity of this inflammatory process in addition to recurrence determines the extent of the structural damage. Other causes of mitral stenosis,

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although less common, include congenital, systemic rheumatic disease (as seen in patients with systemic lupus erythematosus, rheumatoid arthritis) as well as radiation therapy as seen in patients with a history of Hodgkin's lymphoma [25].

Signs and Symptoms

Individuals tend to present with shortness of breath and exertional dyspnea. Due to increased left atrial pressure and resultant pulmonary edema, some patients may present with hemoptysis. Hoarseness and cough due to compression of the recurrent laryngeal nerve by increased left atrial pressure can also be seen. Hoarseness would be part of a constellation of other symptoms as seen in cardiovocal syndrome (Ortner's Syndrome) [26].

Physical Examination

On auscultation, a loud first heart sound can be heard, accompanied by an opening snap and mid-diastolic rumble. This can be best heard at the cardiac apex. Mitral stenosis, when severe, can cause pulmonary hypertension from increased left atrial pressure. Patients with pulmonary hypertension can develop mitral facies, with pink-purplish patches noted on examination due to capillary vasodilation. Patients that develop right heart failure can present with edema. Chest X-ray imaging may show dilated pulmonary vessels, and flattening of left heart border due to left atrial enlargement [27].

Natural History and Complications Medical Therapy and Timing of Surgery

Mitral stenosis is generally slow to progress from asymptomatic to severe. Thus asymptomatic patients can be monitored by echocardiograms. The frequency of echocardiograms is every 3–5 years when the mitral valve area is >1.5 cm squared; then, in severe mitral stenosis, it is every 1–2 years when the mitral valve area is 1.0–1.5 cm squared; then it is once a year when the mitral valve area is <1.0 cm squared [28].

Patients with rheumatic mitral stenosis associated with atrial fibrillation, left atrial thrombus, or prior history of an embolic events should be placed on anticoagulation. Patients with tachycardia at rest or with exertion are considered symptomatic and may benefit from a beta blocker to manage symptoms. Surgical/operative management may be indicated in some instances.

Mitral Regurgitation

Etiology

Mitral regurgitation can be classified as acute versus chronic, and divided into primary versus secondary depending on the etiology.

In primary mitral regurgitation, there is organically or structurally a component of the mitral valve (leaflets, chordae tendinae, annulus, or papillary muscles) that is defective, incompetent, or damaged resulting in backflow during systole. The leading cause of primary mitral regurgitation, and mitral regurgitation in general, is mitral valve prolapse among other degenerative mitral valve diseases. Although uncommon in the USA, rheumatic heart disease often results in mitral regurgitation in the first two decades of life. Other causes of primary mitral regurgitation include infective endocarditis, trauma, mitral annular calcifications, or drug induction [29].

Mitral regurgitation due to secondary causes arise from functional incompetence of the valve, and not due to structural defect. This is typically seen in patients with coronary artery disease or cardiomyopathy. Patients with coronary artery disease, including those with a history of myocardial infarction, can have resultant regional wall motion abnormalities. This leads to improper closure of mitral valve leaflets. In patients with hypertrophic cardiomyopathy, mitral regurgitation can occur due to anterior motion of the mitral leaflets. In dilated cardiomyopathy, findings are a result of dilation of the annulus and displacement of the papillary muscles.

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Signs and Symptoms

In acute mitral regurgitation, patients can present with symptoms of hypotension, pulmonary edema, and cardiogenic shock. Such a scenario would be considered a cardiac emergency and can be seen in patients with infectious endocarditis and inferior myocardial infarction due to rupture of papillary muscles. In chronic mitral regurgitation, there is a compensatory left atrial enlargement and left ventricular dilation that allows for adequate support of cardiac backflow and increased preload. In this setting, patients may not always be symptomatic. In severe cases of chronic mitral regurgitation, patient can present with exertional dyspnea and fatigue. Patients with mitral valve prolapse may complain of palpitations. Although less common than in mitral stenosis, patient may present with hemoptysis, thromboembolism, and symptoms of right heart failure.

Physical Examination

On auscultation, a holosystolic murmur can be heard best at the cardiac apex, with radiation to the axilla. The murmur can be blowing with a high-pitched S3. The murmur is louder with leg raise, squatting, and hand grip, as this increases venous return and arterial pressures. Standing tends to decrease the murmur, as this reduces venous return. Some patients have paroxysmal or persistent atrial fibrillation as a consequence of mitral regurgitation. A midsystolic click followed by systolic murmur can sometimes be heard in patients with mitral valve prolapse [30].

Natural History and Medical Therapy

Some studies show that vasodilators improve hemodynamic compensation in acute mitral regurgitation. They tend to reduce aortic pressure, decrease afterload as well as the regurgitant flow. Timely surgical intervention may still be indicated. Surveillance with echocardiogram is key in closely following for any progressive changes with mitral regurgitation. Echo every 3–5 years for mild mitral regurgitation, every 1–2 years for moderate, and 6–12 months in severe mitral regurgitation [31].

Cardiovascular Evaluation of the Young Athlete

Pre-participation screening of young athletes is used to identify any relevant history, physical findings, or symptoms that would raise concern for sudden cardiac death. Young athletes, defined as those under the age of 35, who suffer from sudden cardiac death (SCD) likely had an underlying structural or nonstructural cardiac condition [32]. Structural causes can arise from congenital coronary anomalies or hypertrophic obstructive cardiomyopathy (HOCM). Nonstructural causes such as in Wolf Parkinson White, Long QT Syndrome, and Brugada Syndrome are other possibilities. Even though SCD is rare, it is important to identify any young athletes at risk and further investigate.

Screening should include a focused history and physical examination. Young athletes should be asked if they have experienced symptoms of chest pain, heart palpitations, exertional dyspnea, presyncopal episodes, or syncope especially in the absence of autonomic prodromal symptoms [33]. Any history of myocarditis, endocarditis, elevated cholesterol, elevated blood pressure, or murmurs should be noted. A thorough family history should be taken to determine if any family members younger than 50 years of age died unexpectedly, or passed away from SCD [34, 35]. On physical examination, murmurs should prompt further workup. Although some connective tissue disorders such as Marfan syndrome have a genetic predisposition, there are some mutations that can arise de novo. As such, general inspection is an important component of any examination. Physical features suspicious for Marfan syndrome such as abnormal arm length to height ratio should prompt further cardiac evaluation.

Obtaining an EKG as part of the pre-participation evaluation is still an ongoing debate. When seen, EKG findings help to solidify a

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diagnosis. In HOCM, EKG findings of left ventricular hypertrophy can be seen. In Wolf Parkinson White, EKG would show shortened PR interval, delta wave, and widened QRS. However, the absence of EKG findings does not rule out the possibility of a cardiac condition, especially in the setting of red flags on history. In some instances, patients with cardiac conditions can have a normal EKG, making history taking a reliable tool in screening young athletes [36].

Even with a thorough history and physical examination, there is the chance of overlooking a patient at risk. Having an automated defibrillator in sight and being CPR certified helps to reduce an adverse outcome in symptomatic patients [37].

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Heart Failure

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Definition

Heart failure (HF) is a syndrome in which the heart is unable to pump blood at a sufficient output to meet tissue requirements, or in which the heart can do so only with an elevated filling pressure. The heart's failure to pump is caused by impairment of cardiac contractility (systolic dysfunction) or cardiac filling (diastolic dysfunction). HF is associated with a variety of interrelated structural, functional, and neurohumoral changes. Structurally, this could result from left ventricle dilation, hypertrophy, or both. Functionally, systolic or diastolic dysfunction can cause reduced ventricular filling or ejection of blood, and to compensate, activation of the sympathetic nervous system and renin-angiotensin-aldosterone systems occurs. These neurohormonal changes increase blood pressure and blood volume, further enhancing venous return (preload), stoke volume, and cardiac output to compensate for the cardiac dysfunction. Despite these compensatory mechanisms, the ability of the heart to contract and relax declines with time. These changes also cause HF symptoms of dyspnea on exertion, fluid retention, and fatigue. Because some patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over "congestive heart failure." Early recognition is important because without appropriate therapies and interventions, HF can progressively worsen [1].

Epidemiology

Heart failure is an ongoing public health challenge in the USA. Americans over 40 years old have a 20% lifetime risk of developing HF [1]. With aging of the population, the prevalence of HF continues to rise over time. An estimated 6.2 million American adults $\geq$20 years of age had HF between 2013 and 2016, compared with an estimated 5.7 million between 2009 and 2012.

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The prevalence of HF will increase 46% from 2012 to 2030, resulting in >eight million people ≥18 years of age with HF [2]. Worldwide, there are an estimated 23 million people with HF [3]. The prevalence of HF is highly variable across the world. Prevalence of HF risk factors also varies worldwide, with hypertension being most common in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa. Ischemic heart disease is most prevalent in Europe and North America. Valvular heart disease is more common in East Asia and Asia-Pacific countries [3]. The overall prognosis of HF is poor with a 50% mortality rate within 5 years of symptom onset. Appropriate management of HF can significantly stabilize the disease with improvement in symptoms, cardiac function, and survival [1].

Hypertensive men and women have a substantially greater risk for developing HF than normotensive men and women [4]. The incidence of HF is greater with higher levels of blood pressure, older age, and longer duration of hypertension. Long-term treatment of both systolic and diastolic hypertension reduces the risk of HF by approximately 50% [4]. Obesity and insulin resistance are also important risk factors for the development of HF. The presence of clinical diabetes markedly increases the likelihood of developing HF in patients without structural heart disease and adversely affects the outcomes of patients with established HF [1]. Fortunately, the appropriate treatment of hypertension, diabetes mellitus, and dyslipidemia can significantly reduce the development of HF.

Classification

HF is classified based on the left ventricular ejection fraction (EF). The echocardiogram will define HF preserved EF (HFpEF) as greater than 50%, mid-range EF (HFmrEF) between 49 and 41%, and reduced EF (HFrEF) as lower than 40% [5]. Symptom severity is graded according to the New York Heart Association (NYHA) functional class designations (class I, no limitation in normal physical activity; class II, mild symptoms only during normal activity; class III, marked symptoms during daily activity, comfortable only at rest; and class IV, severe limitations and symptoms even at rest). While the NYHA classification is a simple way to classify HF symptoms, it is nevertheless a subjective measure affected by the patient and physician expectations. The American College of Cardiology (ACC) and the American Heart Association (AHA) created HF stages that emphasize the progressive nature of HF and defines the appropriate therapeutic approach for each stage. Table 1 demonstrates the overlap and progression of the ACC/AHA stages and NYHA classes [1]. HFrEF has effective evidence-based therapies that improve morbidity and mortality, while HFpEF still lacks the same amount of therapies.

Table 1 Classification of HF: ACC/AHA HF stage and NYHA functional class

ACC/AHA HF Stage[1]		NYHA Functional Class[2]	
High risk, no structural heart disease	A	Not applicable	–
Asymptomatic but with structural heart disease (MI, reduced LVEF, valvular disease)	B	Asymptomatic	I
Current or history of symptomatic HF with cardiac structural abnormalities	C	Symptoms with significant exertion	II
		Symptoms on minor exertion	III
Refractory end-stage heart failure	D	Symptomatic at rest	IV

ACC/AHA American College of Cardiology/American Heart Association, NYHA New York Heart Association, MI Myocardial Infarction, LVEF Left Ventricular Ejection Fraction
*Arrows indicate potential directions of stage progression

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Approach to the Patient

The approach to determining the cause and severity of heart failure (HF) includes the history, physical examination, and diagnostic tests. Initial tests include an electrocardiogram, initial blood tests, echocardiogram, and assessment for coronary artery disease. Demonstration of an underlying cardiac cause is key to the diagnosis of HF. This is usually a myocardial abnormality causing systolic and/or diastolic ventricular dysfunction. However, abnormalities of the valves, pericardium, endocardium, heart rhythm, and conduction can also cause HF (and more than one abnormality is often present). It is crucial to identify the underlying cardiac problem for therapeutic reasons, as the precise pathology determines the specific treatment used.

Diagnosis

History

A detailed history and physical examination should be obtained in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF. Typical symptoms include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and ankle swelling. Other symptoms of right-sided heart failure that may be present but are more nonspecific include abdominal bloating, right upper-quadrant discomfort, and early satiety. In patients with idiopathic dilated cardiomyopathy, a three-generational family history should be obtained to aid in establishing the diagnosis of familial dilated cardiomyopathy [1].

Physical Examination

Patients should be examined for markers of congestion and reduced peripheral perfusion (Table 2). Patients with more signs of congestion (jugular venous distension, edema, lung rales, and S3 gallop) are at higher risk of cardiovascular death or heart failure hospitalization independent of symptoms, natriuretic peptides, and validated risk scores. As a result of compensatory upregulation in lymphatic drainage, patients with chronic HF may lack lung rales or peripheral edema, even when pulmonary capillary wedge pressure is elevated [6]. The clinical assessment of left-sided filling pressures relies heavily on the presence of symptoms (e.g., dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and S3 gallop) and evidence of elevation in right-sided filling pressures (e.g., jugular venous distension, hepatojugular reflux, and edema). Markers of low cardiac output state include diminished peripheral pulses, cool extremities, pallor, peripheral cyanosis, sluggish capillary refill, presence of pulsus alternans, and a low pulse pressure.

Table 2 Initial evaluation for diagnosing symptoms and signs in heart failure with reduced ejection fraction

Typical symptoms
Dyspnea
Orthopnea
Paroxysmal nocturnal dyspnea
Fatigue
Reduced exercise tolerance
Ankle swelling
Cough
Abdominal distension
Wheeze
Abdominal bloating
Early satiety
Bendopnea
More specific signs
Elevated jugular venous pressure
Positive abdominojugular reflux
S3 (gallop rhythm)
Laterally displaced apical impulse
Less specific signs
Lung rales
Peripheral edema
Ascites
Cool and/or mottled extremities
Narrow proportional pulse pressure (pulse pressure: Systolic blood pressure ratio 0.25)
Murmur of valvular regurgitation or stenosis
Weight loss and cachexia (advanced HF)

Modified from Murphy et al. [6]

Laboratory and Imaging

A number of laboratory tests can aid in the diagnosis of HF and can help risk stratify patients with known HF. At the time of diagnosis, laboratory

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work should focus on evidence of end-organ involvement, including assessment of renal function and liver abnormalities. Initial testing involves the measurement of natriuretic peptides, electrocardiography, chest X-ray, and echocardiogram. Further laboratory assessment should be considered based on suspicion of other causes or if findings suggest further investigation (Table 3).

B-Type Natriuretic Peptide

B-Type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to stretching and increased wall tension from volume and pressure overload. Cleavage of the prohormone proBNP produces biologically active BNP as well as biologically inert NT-proBNP. Changes in natriuretic peptide levels in response to HF therapy have been shown to correlate with changes in pulmonary wedge pressure. The measurement of natriuretic peptide levels in patients presenting with dyspnea in the emergency department outperforms clinical judgment for the diagnosis of HF (Table 4). It is important to realize that natriuretic peptides can be elevated in disease processes other than HF (e.g., acute pulmonary embolism, COPD, cor pulmonale, anemia, renal failure, sepsis, atrial fibrillation, and myocardial infarction).

Electrocardiogram

An electrocardiogram (ECG) is a useful initial test to evaluate the heart for structural or physiological abnormalities. An abnormal ECG increases the likelihood of the diagnosis of HF, but has low specificity. It is most useful in evaluating other possible causes of HF or reasons for a worsened clinical status. HF is unlikely in patients presenting with a completely normal ECG (sensitivity 89%) [7]. Therefore, the routine use of an ECG is mainly recommended to rule out HF. Signs of previous MI or ischemia, left ventricle hypertrophy, left bundle branch block (LBBB), or atrial fibrillation can all be present and assist in guiding further treatment options. A LBBB in the presence of HF is a very poor prognostic sign with

Table 3 Laboratory evaluation for heart failure and selected alternate causes

Initial tests
BNP or NTproBNP level (Heart failure)
Complete blood count (Anemia, infection)
Serum electrolytes (Diuretics, cause of arrhythmia)
Liver profile (Hepatic congestion, alcoholism)
Renal function (Renal disease, volume overload)
Thyroid stimulating hormone (Thyroid disorders)
Urinalysis (Renal disease)
Other tests for alternative causes
Arterial blood gases (Hypoxia, pulmonary disease)
Blood cultures (Endocarditis, systemic infection)
Human immunodeficiency virus (Cardiomyopathy)
Lyme serology (Bradycardia/heart block)
Thiamine level (Deficiency, beriberi, alcoholism)
Troponins, creatinine kinase-MB (Myocardial infarction)
Ferritin, iron levels (Hemochromatosis)
Urine or serum drug screen (Cocaine use)
Tests for comorbid conditions, risk management
A1C level (Diabetes mellitus)
Lipid panel (Hyperlipidemia, cardiovascular risk)

Sources: King et al. [21]
BNP B-type natriuretic peptide; *NTproBNP* N-terminal pro-B-type natriuretic peptide

Table 4 Uses of natriuretic peptides as part of the initial evaluation for diagnosing HFrEF

To rule in acute heart failure
NT-proBNP >450 pg/mL BNP >100 pg/mL
To rule out acute heart failure
NT-proBNP <300 pg/mL10 BNP <50 pg/mL
To rule out chronic heart failure
NT-proBNP <125 pg/mL BNP <35 pg/mL
Factors that increase natriuretic peptides
Advancing age Atrial fibrillation or other arrhythmia Kidney failure Weight loss and cachexia (advanced HF)
Factors that decrease natriuretic peptides
Obesity Pericardial constriction

Modified from Murphy et al. [6]
BNP B-type natriuretic peptide; *HFrEF* heart failure with reduced ejection fraction; *NT-proBNP* N-terminal pro–B-type natriuretic peptide

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increased one-year mortality overall and from sudden cardiac death [8]. A QRS interval of >0.12 and a LBBB pattern in a HF patient would be a consideration to refer to a cardiologist or electrophysiologist to evaluate for an implantable device after medical optimization.

Chest Radiograph

A chest radiograph in HF can reveal cephalization, interstitial or alveolar edema, the presence of effusions, or Kerley B lines. The absence of these findings does not rule out HF. Of note, the chest radiograph can help identify other etiologies of dyspnea such as pneumonia, COPD, thoracic mass, or pneumothorax.

Cardiac Imaging

Echocardiography is the most important imaging tool to diagnose HF. It provides assessment of chamber dimensions, biventricular function, valvular stenosis/regurgitation, wall thickness, wall motion, and filling pressures/patterns (diastolic function), including hemodynamics.

Cardiac magnetic resonance imaging, although not readily available, provides high anatomical resolution of all aspects of the heart and surrounding structure, leading to its recommended use in known or suspected congenital heart diseases [1]. It can also evaluate ischemia and identify inflammatory or infiltrative causes of HF without radiation exposure. Cardiac magnetic resonance imaging allows accurate assessment of biventricular function, quantitation of valvular regurgitation and/or stenosis, tissue characterization, and assessment of both microvascular and epicardial perfusion. It can assist in the diagnosis of the underlying etiology of cardiomyopathy, such as infiltrative cardiomyopathies, myocarditis, prior infarction, suggesting an ischemic etiology. Also, a cardiac magnetic resonance is an excellent method to assess myocardial viability in patients with impaired LV function and significant coronary disease when deciding on the utility of revascularization.

Given that 50% of HFrEF cases are of ischemic etiology, patients with a new diagnosis of HFrEF usually require an evaluation for coronary artery disease, although other patient-specific factors (e.g., advanced age, multiple severe comorbidities, noncandidates for revascularization, or choosing not to undergo coronary revascularization procedures) should be considered prior to referral. Coronary angiography is the criterion standard test for identification of obstructive epicardial coronary artery disease, although noninvasive testing with coronary-computed tomography angiography may be considered in patients with low pretest probability for coronary atherosclerosis. Stress testing is less useful because of lower sensitivity and specificity [6].

Special Testing

Hemodynamic monitoring is indicated in patients with clinically indeterminate volume status, those refractory to initial therapy, patients with hypotension, and/or worsening renal function particularly if intracardiac filling pressures and cardiac output are unclear.

To allow physicians to discuss prognostic information with patients and aid in decision-making, a commonly utilized model is the Seattle Heart Failure Model (SHFM). The model also allows the clinician to add or subtract an assortment of treatment regimens, including medical therapies and devices, to assess how these changes affect mortality. There is a simple, free, online score calculator that is readily accessible.

Differential Diagnosis

Patients with HF may present with complaints of decreased exercise tolerance, fluid retention, or both. Many of the symptoms and signs of HF are nonspecific, so other potential causes should be considered such as cardiac and noncardiac causes. Cardiac causes include arrhythmias, structural heart disease, valvular disease, and myocardial infarction. Noncardiac causes include processes that increase the preload (volume overload and renal failure), increase the afterload (hypertension), reduce the oxygen-carrying capacity of the

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blood (anemia, pulmonary diseases), or increase demand (sepsis).

Treatment

In heart failure management, the goals are to reduce mortality and morbidity by improving functional status and health-related quality of life, reducing symptoms, and decreasing the risk of hospitalization [9]. Based on the severity of the illness, nonpharmacologic therapies include dietary sodium and fluid restriction and physical activity as appropriate. Figure 1 shows a treatment strategy for the use of drugs (and devices) in patients with HFrEF. The recommendations for each treatment will be summarized ahead.

Heart Failure with Reduced Ejection Fraction

The standard therapy for HFrEF includes loop diuretics for fluid and symptom control as well as angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or an angiotensin receptor neprilysin inhibitor (ARNI), and beta-blocker therapy,

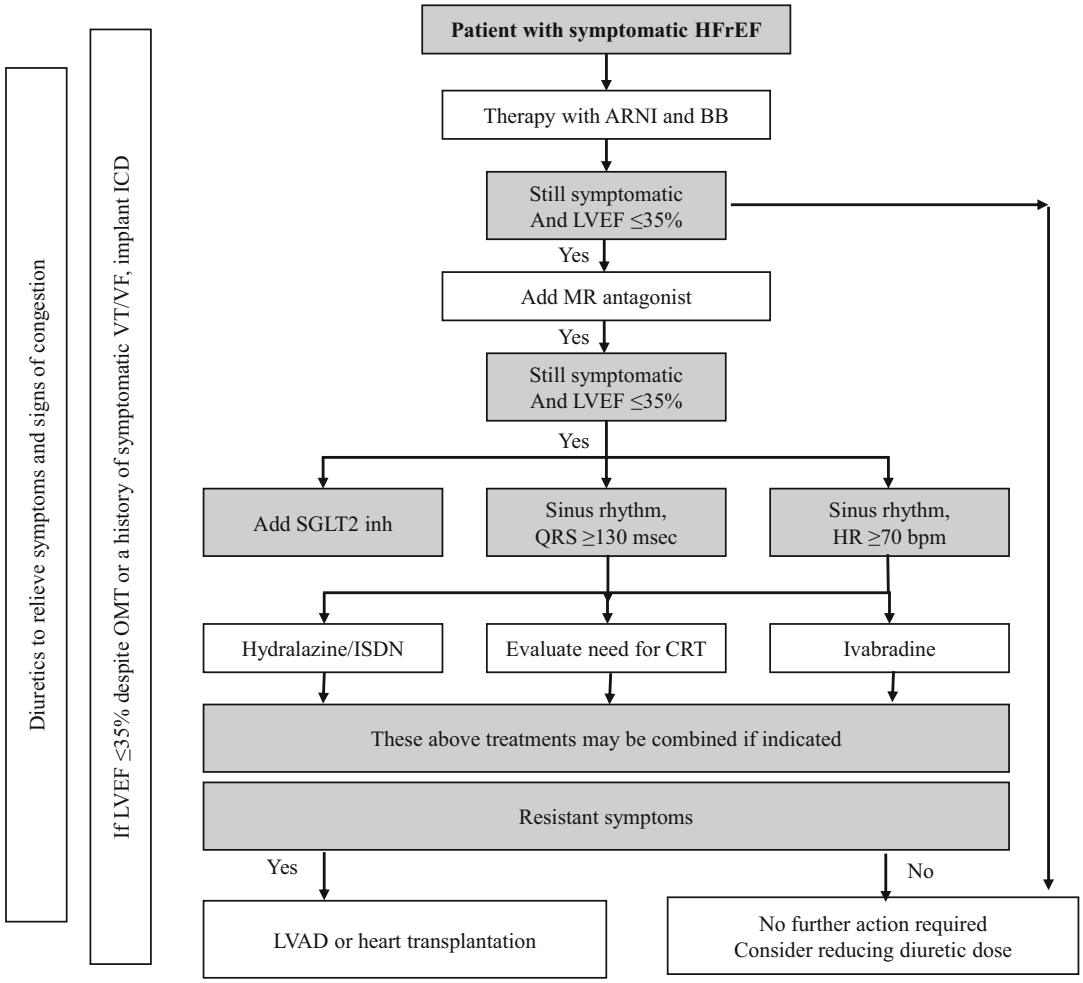


Fig. 1 Therapeutic algorithm for a patient with symptomatic heart failure with reduced ejection fraction. (Modified from Ponikowski P, et al. [22])

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mineralocorticoid receptor antagonist (MRA), and more recently SGLT-2 inhibitors to improve morbidity and mortality. Appropriate starting doses of drug therapies and evidence-based targets are listed in Table 5.

Diuretics

Diuretics are an important treatment for patients with HF and evidence of volume overload. They also have not been proven to have a long-term mortality benefit [1]. The goal of loop diuretic therapy is to manage fluid retention and achieve and maintain a euvolemic state. The majority of HF patients are treated with loop diuretics, such as furosemide, bumetanide, or torsemide. Torsemide has the advantage of greater, and more consistent, bioavailability following oral dosing, Diuretic resistance can be due to inadequate diuretic dose, excess sodium intake, reduced diuretic absorption, impaired diuretic urinary excretion (due to chronic kidney disease, advanced age, or poor cardiac output), and concomitant medications (e.g., nonsteroidal anti-inflammatory agents). Treatment approaches to refractoriness to loop diuretics include increased dose, dividing into multiple daily doses, switching from furosemide to torsemide, and adding a thiazide diuretic, such as chlorothiazide or metolazone. It is important to monitor electrolytes as well as the renal function during titration of diuretics. Initial,

Table 5 Medications in heart failure with reduced ejection fraction

Drugs for mortality and morbidity benefit	Initial doses	Target doses
Angiotensin-converting enzyme inhibitors		
Captopril (Capoten) Enalapril (Vasotec) Fosinopril (Monopril) Lisinopril (Zestril, Prinivil) Perindopril (Aceon) Quinapril (Accupril) Ramipril (Altace) Trandolapril (Mavik)	6.25 mg TID 2.5 mg BID 5–10 mg daily 2.5–5 mg daily 2 mg daily 5 mg BID 1.25–2.5 mg daily 1 mg daily	50 mg TID 10–20 mg BID 40 mg daily 20–40 mg daily 8–16 mg daily 20 mg BID 10 mg daily 4 mg daily
Angiotensin receptor blockers		
Candesartan (Atacand) Losartan (Cozaar) Valsartan (Diovan)	4–8 mg daily 25–50 mg daily 20–40 mg BID	32 mg daily 50–100 mg daily 160 mg BID
β-Blockers		
Bisoprolol (Zebeta) Carvedilol (Coreg) Carvedilol CR (Coreg CR) Metoprolol succinate CR/XL (Toprol XL)	1.25 mg daily 3.125 mg BID 10 mg daily 12.5–25 mg daily	10 mg daily 50 mg BID 80 mg daily 200 mg daily
Aldosterone antagonists		
Eplerenone (Inspra) Spironolactone (Aldactone)	25 mg 2.5–25 mg daily	50 mg daily 25 mg daily or BID
Vasodilators: Hydralazine and isosorbide dinitrate		
Fixed dose hydralazine and isosorbide dinitrate (BiDil) Hydralazine and isosorbide dinitrate (Apresoline and Isordil)	37.5 mg/20 mg TID 25–50 mg and 20–30 mg TID or QID	75 mg/40 mg TID 300 mg and 120 mg daily in TID doses
Angiotensin receptor neprilysin inhibitor		
Sabubitril/Valsartan (Entresto)	49 mg/51 mg BID	97 mg/103 mg BID
SGLT-2 inhibitors		
Dapagliflozin (Farxiga) Empagliflozin (Jardiance)	10 mg daily 10 mg daily	10 mg daily 10 mg daily

Modified from: Maddox et al. [14]
BID twice daily; *TID* three times daily; *QID* four times daily

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Table 6 Diuretic dose therapies

Drugs for symptom control		Initial doses	Maximum doses
Loop diuretics	Drug/Dose equivalents		
Bumetanide (Bumex) Furosemide (Lasix) Torsemide (Demadex)	1 mg PO/1 mg IV 40 mg PO/80 mg IV 20 mg PO/20 mg IV	0.5–1.0 mg/dose 20–40 mg/dose 5–10 mg/dose	10 mg/day 600 mg/day 200 mg/day
Thiazide diuretics (Combination with loops)			
Hydrochlorothiazide (HydroDiuril) Metolazone (Zaroxolyn)		25 mg daily 2.5 mg daily	100 mg daily 10 mg daily

Modified from: Yancy et al. [1]

maximum, and equipotent oral and intravenous (IV) dose equivalents are listed in Table 6.

Renin-Angiotensin System Inhibition

Renin-angiotensin system inhibition with ACE Inhibitor, ARB, or ARNI angiotensin-converting enzyme inhibitors (ACEI) reduce morbidity and mortality in HFrEF. Clinical trials clearly establish the benefits of ACEI in patients with mild, moderate, or severe symptoms of HF. ACEI can produce angioedema and should be given with caution to patients with low systemic blood pressures, renal insufficiency, or elevated serum potassium. They also inhibit kininase and increase levels of bradykinin, which can induce cough but also may contribute to their beneficial effect through vasodilation [10].

Angiotensin receptor blockers (ARBs) do not inhibit kininase and are associated with a much lower incidence of cough and angioedema than ACE inhibitors. Long-term therapy with ARBs produces hemodynamic, neurohormonal, and clinical effects consistent with those expected after interference with the renin-angiotensin system and have been shown to reduce morbidity and mortality, especially in ACE inhibitor–intolerant patients.

In ARNI, an ARB (valsartan) is combined with an inhibitor of neprilysin (sacubitril), an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. In a landmark trial that compared the first approved ARNI, valsartan/sacubitril, with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB, the ARNI reduced the composite endpoint of cardiovascular death or HF hospitalization significantly, by 20% [11]. The benefit was seen to a similar extent for both death and HF hospitalization and was consistent across subgroups. The use of ARNI is associated with the risk of hypotension and renal insufficiency and may lead to angioedema as well.

Beta-Blockers

Use of beta-blockers is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality [1]. Carvedilol (Coreg), metoprolol succinate (Toprol XL), and bisoprolol (Zebeta) are recommended and have proven mortality benefits over other beta-blockers likely due to how they inhibit the sympathetic nervous system which is activated in HF. Even among these three proven beta-blockers, there are some differences. Beta-blockers benefit mortality and disease progression in addition to ACEI therapy and are recommended early after the diagnosis of HFrHF with initiation at low doses along with low-dose ACEI and appropriate titration (Table 5). Beta-blockers should be hemodynamically stable with minimal to no fluid retention before initiation and are contraindicated with bradycardia, hypotension, hypoperfusion, second- or third-degree atrioventricular block, or severe asthma or COPD [1].

Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists (MRA) are recommended in patients with NYHA class

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II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity, mortality, and HF hospitalization. MRA block receptors bind aldosterone and, with different degrees of affinity, other steroid hormone (e.g., corticosteroids and androgens) receptors. Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels >5.0 mmol/L. Regular checks of serum potassium levels and renal function should be performed according to clinical status.

Hydralazine and Isosorbide

The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta-blockers, unless contraindicated [1]. It can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB or ARNI because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.

Ivabradine

Ivabradine is an agent that selectively inhibits current in the sinoatrial node, providing heart rate reduction without affecting blood pressure, myocardial contractility, or intracardiac conduction. Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF who are receiving guideline medical therapy, including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest [10].

Digoxin

Digoxin may be considered in patients in sinus rhythm with symptomatic HFrEF to reduce the risk of hospitalization (both all-cause and HF hospitalizations) [5]. Digoxin level should be monitored a week after initiation for a goal level less than 1 ng/mL, also toxicity risk is higher in the elderly, causing hypomagnesemia, hypokalemia, and renal dysfunction.

New Therapies Awaiting Guideline Recommendation

SGLT-2 Inhibitors

The US Food and Drug Administration recently approved the use of dapagliflozin for treatment of HFrEF, irrespective of diabetes status, and it is anticipated that dapagliflozin will be added to guideline-directed medical therapy for all patients with HFrEF in the 2021 American College of Cardiology/American Heart Association heart failure guideline [6]. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial evaluated the effect of dapagliflozin in patients with HFrEF with and without type 2 diabetes [12]. Dapagliflozin reduced the primary end point of worsening heart failure or cardiovascular death, cardiovascular mortality, and all-cause mortality compared with placebo. SGLT2 inhibitors are contraindicated in patients with type 1 DM, type 2 DM with risk factors for ketoacidosis, or severely impaired or rapidly declining kidney function. In the DAPA-HF trial, dapagliflozin demonstrated a reduction in CV death and HF hospitalization in patients with and without type 2 diabetes (T2D) [12]. In addition, the EMPEROR-reduced (Empagliflozin Outcome Trial in Patients with Chronic HFrEF) trial demonstrated a reduction in HF hospitalization/CV death from empagliflozin treatment in patients with HFrEF with and without diabetes [13]. As such, it is clear that SLGT2 inhibitors exhibit a beneficial class effect in patients with HFrEF.

Vericiguat

Vericiguat is an oral soluble guanylate cyclase stimulator that increases activity of the second messenger cyclic guanosine monophosphate

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(cGMP), which is involved in regulation of protective cardiovascular, kidney, and metabolic actions. The VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial enrolled patients with higher-risk HFrEF than those included in other contemporary clinical trials, and found that vericiguat reduced the composite primary outcome of cardiovascular death or first heart failure hospitalization over median follow-up of 10.8 months, although this was driven by the reduction in heart failure hospitalization [15]. Given its vasodilation properties, vericiguat resulted in symptomatic hypotension in 9.1% of patients, although these were not significantly higher than placebo.

Omecantiv Mecarbil

This is a novel cardiac myosin activator, or myotrope – significantly reduces the combined risk of first heart failure events or cardiovascular death in patients with chronic HFrEF, as shown in the GALACTIC-HF trial [16]. The benefit was modest, with an absolute reduction of 2.1% and a relative reduction of 8% over a median follow-up of about 22 months. One of the benefits is that it is well tolerated and does not affect the blood pressure nor the heart rate.

How to Initiate Therapies

The ACC Expert Consensus recommends titration of therapies as follows: In a patient with new-onset stage C HFrEF, the writing committee recommends that either an ARNI/ACEI/ARB or beta-blocker should be started. In some cases, an ARNI/ACEI/ARB and a beta-blocker can be started at the same time. Regardless of the initiation sequence, both classes of agent should be up-titrated to the maximum tolerated or target doses in a timely fashion (every 2 weeks). Initiation of an ARNI/ACEI/ARB is often better tolerated when the patient is still congested, whereas beta-blockers are better tolerated when the patient is less congested with an adequate resting heart rate; beta-blockers should not be initiated in patients with decompensated signs or symptoms. Only evidence-based beta-blockers (bisoprolol, carvedilol, and metoprolol succinate) should be used in patients with HFrEF. With recent clinical trial data supporting the use of SGLT2 inhibitors in a reasonably broad spectrum of HFrEF severity, the addition of this class of therapy to the regimens of patients with HFrEF provides improvements in clinical outcomes and in patient-reported outcome measures [14].

Adverse Therapies

Non-dihydropyridine calcium channel blockers (CCBs) are not indicated for the treatment of patients with HFrEF. Diltiazem and verapamil have been shown to be unsafe in patients with HFrEF. There is a variety of dihydropyridine CCBs; some are known to increase sympathetic tone and they may have a negative safety profile in HFrEF. There is only evidence on safety for amlodipine [5].

Implantable Devices

Implantable cardioverter defibrillators (ICDs) are effective in preventing bradycardia and correcting potentially lethal ventricular arrhythmias. Sudden cardiac death (SCD) from cardiac arrest and ventricular arrhythmias is estimated to occur in a third to half of all HF deaths, thus automatic ICDs are indicated. ICD implantation is recommended only after a sufficient trial (minimum 3 months) of optimal medical therapy (OMT) has failed to increase the LVEF to 35% [1]. In primary prevention, ICDs are recommended for HF patients with a reasonable life expectancy (>1 year), no history of recent MI (within 40 days), NYHA Class II–III and a LVEF ≤35%, or NYHA Class I and a LVEF <30% [1]. In secondary prevention, ICDs are recommended for patients with history of cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia regardless of the EF [1]. Multiple studies have proven the benefit in NYHA Class II–III reducing mortality by 23–31%. Subcutaneous defibrillators may be as effective as conventional ICDs with a

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lower risk from the implantation procedure. They may be the preferred option for patients with difficult access or who require ICD explantation due to infection. A wearable ICD (an external defibrillator with leads and electrode pads attached to a wearable vest) that is able to recognize and interrupt VT/ventricular fibrillation may be considered for a limited period of time in selected patients with HF who are at high risk for sudden death but otherwise are not suitable for ICD implantation. However, no prospective randomized clinical trials evaluating this device have been reported [5].

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) involves implantation of pacing leads to the right and left ventricles via the coronary sinus, which are timed to pace at an interval maximizing synchrony. CRT is indicated for patients with NYHA Class III or IV symptoms, a LVEF $\leq$35%, a QRS interval $\geq$ 0.15 ms, a left bundle branch block (LBBB) pattern, and sinus rhythm to improve mortality and hospitalizations. Studies of CRT include dNYHA Class II, a QRS $\geq$0.12 ms, or a non-LBBB pattern, resulting in varying mortality and hospitalization decreases from 19% to 37%. CRT also improves symptoms and quality of life in these studies. Patients who meet criteria for CRT and an ICD should receive a combined device, unless contraindicated [1].

Transcatheter Mitral Valve Repair

Transcatheter mitral valve repair (tMVR) may be considered for patients with HFrEF and severe secondary mitral regurgitation (MR) after the use of maximally tolerated guideline-directed medical therapy [17]. In the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, there was a significant reduction in the primary end point of heart failure hospitalization and the secondary end point of all-cause mortality in patients treated with tMVR compared with placebo.

Wireless Pulmonary Artery Pressure

Patients with persistent NYHA class III symptoms may be considered for implantation of a wireless pulmonary artery pressure monitor. In the CHAMPION trial, the device reduced heart failure hospitalizations, and there was a statistically nonsignificant reduction in mortality over a mean follow-up period of 18 months [6].

Cardiac Rehabilitation

A prescribed exercise training program modestly reduced clinical events when added to optimal medical therapy. After adjustment for prognostic variables, the risk of all-cause mortality and hospitalization was 11% lower in cardiac rehabilitation participants, and cardiovascular mortality and heart failure hospitalization was reduced by 15%. Cardiac rehabilitation was safe, with no excess risk of cardiovascular adverse events or hospitalization after exercise [6].

Heart Failure with Preserved Ejection Fraction

HFpEF has been defined by the European Society of Cardiology (ESC) as preserved left ventricular EF (LVEF $\geq$50%), with evidence of diastolic dysfunction or structural heart disease, in the context of classic signs and symptoms of heart failure and elevated natriuretic peptides [5]. HFpEF represent about a third to one-half of the total number of HF patients [18].

The H2FPEF score and the HFpEF nomogram are recently validated highly sensitive tools employed for risk assessment of subclinical heart failure. These tools are based on clinical and echocardiographic parameters, including body mass index (BMI) > 30 kg/m2 (H); use of two or more antihypertensive medications (H); the presence of atrial fibrillation (F); pulmonary hypertension (pulmonary artery systolic pressure > 35 mmHg) (P); elderly with an age > 60 years (E); and elevated filling pressures ($E/e' > 9$) [18]. With a score of 0–1 consider a

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noncardiac cause, a score of 2–5 with abnormal natriuretic peptides and abnormal wedge pressure, or a score of 6–9 is diagnostic of HFpEF.

Clinical trials in HFpEF have produced largely neutral results to date and most management is directed toward associated conditions (e.g., hypertension) and symptoms (e.g., edema). Overall with HFpEF, no treatment has been well validated to show a reduction in morbidity and mortality. The treatment of HFpEF is directed by management of associated conditions (e.g., hypertension, atrial fibrillation, sleep apnea, obesity, and diabetes) and symptoms [1]. Amyloidosis is also an increasingly common cause of HFpEF and must be excluded in patients suspected of HF [18]. In the near future, SGLT2 inhibitors trials will be showing results in this patient population.

Acute Heart Failure

Acute heart failure (AHF) refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment [5]. AHF may present as a first occurrence, or, more frequently, as a consequence of acute decompensation of chronic HF, and may be caused by primary cardiac dysfunction or precipitated by extrinsic factors, often in patients with chronic HF. Acute myocardial dysfunction (ischemic, inflammatory, or toxic), acute valve insufficiency, or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF. Clinical classification is based on bedside physical examination in order to detect the presence of clinical symptoms/signs of congestion (wet versus dry) and/or peripheral hypoperfusion (cold versus warm). Initial diagnosis of AHF should be based on a thorough history assessing symptoms, prior cardiovascular history and potential cardiac and noncardiac precipitants, as well as on the assessment of signs/symptoms of congestion and/or hypoperfusion by physical examination and further confirmed by appropriate additional investigations such as ECG, chest X-ray, laboratory assessment (with natriuretic peptides biomarkers), and echocardiography. An arterial blood gas and lactic acid are warranted to accurately assess acid-base abnormalities and hypoxia. Invasive hemodynamic monitoring can be considered when there is evidence of impaired perfusion, uncertainty of fluid status, uncertainty of systemic or pulmonary vascular resistance, worsening renal function, or a need for vasoactive agents [1].

The initial goal of treatment should be stabilization to control hypoxemia or hypotension that can cause under perfusion of vital organs, the heart, kidneys, and brain [5]. Intravenous loop diuretics are the first-line therapy to treat pulmonary edema and volume overload by lowering central venous capillary wedge pressures and improving hemodynamic status. Loop diuretic dosing should be equal or 2.5 times higher than the patient's normal oral dose (for dosing and equivalents, see Table 6). A continuous infusion of loop diuretics is not more effective than IV bolus therapy. If necessary, adding a second diuretic to potentiate a diuresis is an option, either with oral hydrochlorothiazide, metolazone, or spironolactone. Careful monitoring of congestive symptoms, volume status, blood pressure, oxygenation, daily intake and out-take, and daily weights should be utilized. To reduce adverse effects of treatment, daily monitoring of renal function, for overdiuresis or azotemia, and electrolyte disturbances to appropriately replace depleted potassium and magnesium is considered [1]. Intravenous vasodilators, nitroglycerin or nitroprusside, are recommended for persistent congestive symptoms and rapid symptom relief in acute pulmonary edema or severe hypertension not responding to diuretics alone [19]. Inotropic agents such as dobutamine or milrinone are indicated in AHF when LVEF is reduced and hypotension causes diminished perfusion and end-organ dysfunction (low-output syndrome). When initiating a vasodilator or inotropic therapy, consideration should be given for cardiology or pulmonary consultation. In patients with HFrEF experiencing a symptomatic exacerbation of HF requiring hospitalization during chronic maintenance treatment with guideline-directed medical therapy (GDMT), it is recommended that GDMT be continued in the absence of hemodynamic instability or contraindications [1].

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Referrals

Early identification and timely referral of select patients to a heart failure specialist is critical so that those with advanced disease can be considered for heart transplantation or LVAD placement. This window of opportunity is missed if referral is delayed until multiorgan failure develops, as such patients may no longer candidates for these therapies. A useful acronym "I-NEED-HELP" was developed to assist clinicians recognize such appropriate patients [20] (Table 7).

Counseling and Patient Education

HF management and self-care behavior are complicated by ageing, comorbid conditions, cognitive impairment, frailty, and limited social support. HF is also a leading cause of hospital admission in the older adult, where it is associated with increased hospital length of stay and risk of mortality [9]. Counseling patients with HF education and strategies for self-care are critically important to enhance treatment compliance, improve transitions of care and manage worsening signs and symptoms of fluid retention. Although frequently utilized, there is limited evidence to support the daily 2–3 gram sodium restriction or the 1.5–2 L fluid restriction recommended by current guidelines. Daily weights are important to detect early fluid retention, and a weight gain of 2 lb. in a day or $\geq$ 5 lb. in a week should prompt contacting or seeing a health care provider. Exercise training or regular physical activity is highly recommended as safe and effective to improve symptoms and functional status. Formal cardiac rehabilitation can be useful and effective when clinically stable to improve functional capacity, exercise duration, quality of life, and mortality [9].

Table 7 When to refer to advanced heart failure

I	IV inotropes
N	NYHA III/IV or persistently elevated natriuretic peptides
E	End organ dysfunction
E	Ejection fraction $\leq$35%
D	Defibrillator shocks
H	Hospitalizations >1
E	Edema despite escalating diuretics
L	Low BP, high heart rate
P	Prognostic medication – Progressive intolerance or down-titration of GDMT

Modified from Yancy et al. [20]

Prevention

Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization [1]. Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the health care team, appropriate dietary and physical activities, and compliance with secondary prevention guidelines for cardiovascular disease. Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life [1].

Management of HF often entails adherence to a complex medication regimen in conjunction with dietary sodium restriction and limitation of fluid intake. In addition, HF usually occurs in the context of one or more comorbid conditions, such as hypertension, diabetes mellitus, and coronary artery disease, which further increase the complexity of care. A significant proportion of early HF readmissions are due to nonadherence to medications or diet, inadequate patient education, or lack of timely follow-up. Heart failure disease management (HFDM) is an opportunity to provide a patient-centered, multidisciplinary, coordinated approach to care that incorporates optimization of the medication regimen, effective patient education, and close follow-up designed to improve clinical outcomes, including quality of life, readmission rates, and survival. Performance measures based on professionally developed clinical practice guidelines should be used with the goal of improving quality of care for HF [1].

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Cardiovascular Emergencies

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Andrea Maritato and Francesco Leanza

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General Principles

Cardiovascular death remains the number one cause of death in the United States. It causes more deaths than lung cancer, breast cancer, prostate cancer, colon cancer, stroke, and chronic lower respiratory diseases combined [1, 2]. While most of these conditions require specialist care, often in a hospital setting, patients will present with these complaints to their family physician, and one must be able to recognize and assess them. Furthermore, family physicians will continue to care for these patients as they live with these conditions. These patients will turn to their family physician for information, second opinions, and advice. This chapter will look at some of these conditions.

Cardiogenic Shock

Shock is caused when oxygen demand exceeds available supply. This can be caused by increased demand of tissue due to infection, metabolic or endocrine disease, decreased supply due to hypovolemia, or a combination of the two. Sometimes, inability of tissue to use oxygen can contribute as well.

There are five categories of shock: cardiogenic, obstructive, hypovolemic, distributive, and endocrine (see Table 1).

When oxygen supply to tissues is decreased, cells can extract more oxygen from red blood cells to meet demands. However, this can only compensate so much, and once supply drops below a critical level, this mechanism can no longer meet the demands of the tissues (compensated vs decompensated shock).

Cardiogenic shock is due to primary cardiac dysfunction. While there may be adequate volume, the heart is unable to circulate it, and tissues suffer from hypoperfusion and hypoxia.

Myocardial infarction (MI) is the most common cause of cardiogenic shock. Arrhythmias, valve rupture, myocarditis, endocarditis, cardiomyopathy, and contusion after chest wall trauma can cause cardiogenic shock as well [3].

Pathophysiology

Ischemia reduces both contractility and relaxation of the heart. This leads to reduced cardiac compliance and reduced filling. As a result, stroke volume is reduced. This in turn reduces cardiac output (cardiac output = stroke volume X heart rate), which then reduces blood pressure. Compensatory mechanisms such as the sympathetic nervous system and the renin-angiotensin system increase heart rate, afterload, and fluid retention. These in turn cause increased oxygen demand on the heart which already has an inadequate supply [4]. This further widens the gap between oxygen need and available oxygen, exacerbating shock and end-organ dysfunction.

Definition

Cardiogenic shock is defined as a systolic BP < 80–90 mmHg in the absence of hypovolemia and must be associated with end-organ damage such as cold extremities, oliguria, or mental status changes. This can also be measured as reduced cardiac index (CI) < 2.2 l/min/m^2 (cardiac output to body surface area)

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Table 1 Shock classification

Name	Causes	Examples
Cardiogenic	Myocardial disease	MI Myocarditis
Obstructive	Mechanical blockage of blood flow beyond the heart	Pulmonary embolus Cardiac tamponade
Hypovolemic	Loss of circulating volume	Blood loss Third spacing
Distributive	Vasodilation and relative inadequate circulating volume	Sepsis Neurogenic shock Anaphylaxis
Endocrine	Thyroid disease Adrenal insufficiency	Thyroid storm Stopping steroid use abruptly

or elevated pulmonary capillary wedge pressure > 15 mmHg [4].

Despite numerous advances in revascularization, medications, and mechanical support, cardiogenic shock is still the number one cause of mortality due to acute myocardial infarction (AMI). Overall, however, the rate of cardiogenic shock has decreased from around 7.5% (range 5–15%) in the 1970s to around 4% in 2003 [5].

Patients who develop cardiogenic shock during a hospitalization for AMI are more than ten times more likely to die than patients hospitalized for AMI who do not develop cardiogenic shock.

Patients who develop cardiogenic shock after an AMI tend to be older, be female, and have a do-not-resuscitate (DNR) order, a history of diabetes mellitus (DM), a history of heart failure (HF), or prior MI.

Management

If a patient develops cardiogenic shock from any cause, the keys to management are improving perfusion and oxygenation. Ideally, PaO_2 (partial pressure of arterial oxygen) levels should be maintained at more than 60 mmHg using bilevel positive airway pressure (BPAP) or intubation as needed. Maintain hemoglobin >8 to allow for adequate oxygen delivery. Fluid resuscitation needs to be monitored carefully as improving filling pressures is important but must be balanced against fluid overload.

Vasopressors such as norepinephrine (Levophed), dopamine, and dobutamine and intraaortic balloon pump counterpulsation (IABP) are used to give BP support while stabilizing and preparing the patient for revascularization procedures. While dopamine was originally considered the first-line vasopressor in cardiogenic shock, recent evidence suggests better outcomes with norepinephrine. Dobutamine doesn't help hypotension and should only be used in patients who have less hypotension, i.e., SBP > 80 mm Hg, in conjunction with vasodilators [6].

Results from the GUSTO-I and SHOCK trials suggest improved survival with emergent revascularization in patients with cardiogenic shock. Percutaneous coronary interventions (PCI) have a class 1A indication in AMI with cardiogenic shock as do coronary artery bypass grafts (CABG) if the patient has suitable coronary anatomy [5]. A class 1A indication means that there are multiple randomized controlled trials showing that the procedure is both effective and useful.

Cardiopulmonary Resuscitation (CPR)

CPR was developed in the 1960s and has been saving lives ever since.

Every 5 years, the International Consensus of CPR and Emergency Cardiovascular Care (ECC) Conference convenes and evaluates the guidelines. The most recent conference took place in 2015, and the American Heart Association (AHA) guidelines for CPR and ECC were updated.

In a major shift, the usual "A-B-C" (airway-breathing-circulation) protocol was changed to "C-A-B" (circulation-airway-breathing). This change was made to stress that reduced time to first compressions and early use of a defibrillator are the priorities for survival. The AHA has found

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that oxygen demand is lessened during cardiac arrest, and therefore pumping blood to a victim's brain is more important than oxygen [7]. In fact, bystander hands-only CPR, where compressions are done without breaths, shows similar outcomes to conventional CPR in adults [8].

The compression rate has been changed from "at least 100 compressions a minute" to "no slower than 100 compressions per minute and no faster than 120 compressions per minute" [9].

Compression depth is now 2 in. for adults as opposed to 1½–2 in. for adults. The depth has changed for children as well [10]. The latest recommendations also suggest not compressing further than 2.4 in. for adults [9].

Minimizing interruptions to compressions is also emphasized by changes in pulse checks. These should not last for more than 10 s, and if an obvious pulse isn't noted, compressions should continue. Again, trying to confirm a faint pulse may delay in needed compressions, and there are rarely significant injuries caused by chest compressions to patients who were not in cardiac arrest.

Additional changes include the removal of atropine (AtroPen) from the pulseless electrical activity (PEA) and asystole protocol.

Waveform capnography has been added to confirm endotracheal tube placement and quality of compressions. Cricoid pressure is no longer recommended during airway management.

Therapeutic hypothermia has been shown to improve outcomes for comatose patients after out-of-hospital arrests with a presenting rhythm of ventricular fibrillation (VF). New evidence shows a wider range of temperatures are acceptable. Providers should select a temperature between 32 and 36 degrees Celsius and maintain it for at least 24 h [9].

Aortic Dissection

Classification

There are two classification systems used: DeBakey and Standford (see Tables 2 and 3).

Table 2 DeBakey classifications

Type I	Originates in the ascending aorta and propagates to at least the arch
Type II	Originates in and is confined to the ascending aorta
Type IIIA	Dissection tear only in the descending thoracic aorta
Type IIIB	Tear extending below the diaphragm [12]

Table 3 Stanford classifications

Type A	All dissections that involve the ascending aorta
Type B	All dissections that do not involve the ascending aorta

Additionally, there are newer classifications based on other characteristics that pertain to suitability for endovascular repair, in particular, the DISSECT mnemonic: duration of dissection (D) less than 2 weeks, 2 weeks to 3 months, and more than 3 months from initial symptoms; intimal tear location (I) in the ascending aorta, arch, descending, abdominal, or unknown; size of the aorta (S); segmental extent (SE); clinical complications (C) such as aortic valve compromise, tamponade, rupture, and branch malperfusion; and thrombosis (T) of the false lumen and the extent [12].

There are three syndromes included in acute aortic disease: aortic dissection, aortic intramural hematoma (IMH), and penetrating atherosclerotic ulcer (PAU). Aortic dissections comprise 90% of acute aortic disease. Classic aortic dissection occurs when there is an intimal flap between the true lumen and the false lumen. An IMH occurs when there is bleeding into the aortic wall without a tear. This occurs by rupture of the vasa vasorum into the media of the aortic wall. This can happen either spontaneously or by a penetrating atherosclerotic ulcer [11].

Aortic dissection is often seen later in life, occurring after age 50. In cases that occur in younger patients, physicians should consider underlying connective tissue disorders such as Marfan's syndrome, Ehler-Danlos syndrome, or familial forms of dissection.

Chronic hypertension is the number one cause of aortic dissection and occurs in 75% of cases. Smoking, dyslipidemia, direct blunt trauma, and

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cocaine and methamphetamine use can all contribute to aortic dissection [12].

Aortic dissection is twice as prevalent in men as women. The incidence is hard to determine as patients may die before reaching care but is estimated to be between 2 and 3.5 cases per 100,000 patient-years [13].

Symptoms

More than 90% of patients with aortic dissection present with pain. Of the patients that present with pain, 90% describe it as severe. The pain is abrupt and maximal at outset and is described as sharp, tearing, or stabbing. Some patients may have uncommon presentations which can confound the diagnosis. They may present with acute heart failure, stroke, or syncope and either not have pain or not mention pain due to other distracting symptoms.

Type A dissections occur in 65% of cases and are more commonly seen in patients between 50 and 60 years of age. Type A dissections are lethal with a 1–2% mortality rate per hour after onset of dissection. Patients usually have symptoms of immediate, severe chest pain and/or back pain. Patients can also have abdominal pain, syncope, and/or stroke. Acute heart failure is also possible if the dissection involves the aortic valve. Type A dissections are surgical emergencies. Medical treatment alone results in approximately 20% mortality in the first 24 h. Mortality increases as time passes, with 50% mortality by day 30. Surgery improves chance of survival, but the 24-h mortality is still high at 10%.

Type B dissections occur more commonly over age 60. Type B dissections have similar presentations with chest and back pain as the common symptoms. Type B dissections are treated medically, and uncomplicated type B dissections have 10% mortality at day 30 [14].

Diagnosis

A routine chest x-ray (CXR) will be abnormal in 60–90% of patients, but 12–15% of patients can have normal CXR, and this cannot be used to exclude the diagnosis.

Electrocardiography (ECG) may be completely normal or extremely abnormal if the dissection involves the coronary circulation. This too cannot be used to exclude the diagnosis.

According to the International Registry of Acute aortic Dissection (IRAD) which is a clearinghouse of information on aortic dissections, transthoracic echocardiography (TTE), or transesophageal echocardiography (TEE), was used as the initial imaging test in 33% of patients, computed tomography (CT) in 61%, magnetic resonance imaging (MRI) in 2%, and angiography in 4%. For confirmation or further evaluation, TTE/TEE was used in 56% of patients, CT in 18%, MRI in 9%, and angiography in 17% [14].

CT is useful for allowing clinicians to evaluate involvement of surrounding organs, local anatomy, and possible ruptures or leaks. However, CT must be done with contrast in order to detect a false lumen and is contraindicated in patients with nephropathy. Contrast-induced nephropathy is a complication even for patients without underlying renal disease. CT imaging is limited by cardiac motion artifact as well as streak artifact from any implanted devices.

MRI is better than CT at seeing the aortic valve and coronary arteries. It does not require radiation or iodinated contrast material. However, MRI is not readily available in all sites and requires the patient to undergo imaging for a longer period of time. Also certain medical devices make it impossible to use MRI [13].

TTE has excellent specificity in the range of 93–96%, but the sensitivity is lower at only 77–80%. As such, a normal TTE does not rule out an aortic dissection. TEE, on the other hand, has both excellent sensitivity at around 98% and specificity at around 95%. Like all ultrasonography, both modalities are operator dependent [13]. This may be a concern in smaller centers where aortic dissection isn't diagnosed frequently.

Additionally, biomarkers are now being looked at for information regarding aortic dissection as it is a disease of the medial layer of the aorta. Currently, only D-dimer has any clinical value though other biomarkers are being studied. D-dimer has a sensitivity of 97% and a specificity of 47%. Therefore, a negative D-dimer may exclude the disease [12].

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Management

Initial management for any type of dissection should include stabilizing the patient, controlling pain, lowering blood pressure, and reducing left ventricular contraction with beta-blockers. Initial blood pressure management is aimed at getting systolic blood pressure < 130 mmHg. IV beta-blockers are the first-line therapy. These should be used to control heart rate as well, aiming for a pulse <60 BPM. Nitroprusside (Nipride, Nitropress) can be used but only in conjunction with beta-blockers as nitroprusside can increase LV contractility. If a patient has a contraindication to a beta-blocker, verapamil (Calan, Isoptin SR, Veralan) or diltiazem (Cardizem, Cartia XT, Dilacor XR, Dilt-CD, Taztia XT, Tiazac) can be used. While stabilizing the patient, additional management depends on whether the patient has a type A or type B dissection.

Type A Dissections

Type A dissections should be managed as surgical emergencies. Medical management of type A dissections has a 20% mortality rate in the first 24 h and 30% in the first 48 h. Surgical management leads to improved outcomes for these patients. The aim of surgical management is to prevent aortic rupture, pericardial effusions which can lead to cardiac tamponade and death, and aortic regurgitation which can impair coronary artery blood flow leading to myocardial infarction and death. At 30 days, the mortality rate for type A dissections managed surgically is between 17% and 26%. If managed medically, the 30-day mortality is between 55% and 60% [13, 15]. The patient's hemodynamic stability immediately prior to surgery is a key predictor of how well the patient will do during and after surgery. Therefore, it is critical that surgery not be delayed for type A dissections.

Type B Dissections

Type B dissections have traditionally been managed medically. Uncomplicated type B dissections should be managed medically, and those that only require medical management have a low mortality rate around 6%. Additionally, the 5-year survival rate for these patients with optimal medical management is 89% [15]. The overall mortality rate for type B dissections treated medically was 10.7% in the International Registry of Acute aortic Dissection (IRAD), while those requiring surgery had a 31% mortality rate. Surgical management is required for complications such as limb ischemia, impending or actual rupture, increasing aortic diameter, intractable pain, or retrograde dissection (type A). Looking at 571 patients in the IRAD with type B dissection, 32% were complicated. The type of surgery required affected the mortality rate for type B dissections requiring surgery. Open surgical repairs had 33% mortality, whereas those who had an endovascular repair had only an 11% mortality rate [13]. As a result, endovascular procedures have a 1A recommendation for surgical repair of complicated type B dissections [14A]. About 25% of type B dissections are complicated at presentation [15].

Almost all patients with a type B dissection require intravenous antihypertensives with most requiring more than one antihypertensive medication during hospitalization. Beta-blockers, calcium channel blockers, nitroglycerin (Nitrolingual, NitroMist, Nitrostat), and nitroprusside were the most common initial antihypertensives used in one study of 129 patients. Mean hospital stay is more than 2 weeks with most patients spending a week in the intensive care unit as well [16]. All patients went home on an oral antihypertensive medication. These patients should be closely followed for at least the first 6 months after discharge as most complications that require intervention occur within this time frame. These patients are at risk for future dissections, aneurysms, and rupture. Systemic hypertension, advanced age, aortic size, and a patent false lumen are characteristics that put patients at higher risk for complications. Estimates are that 1/3 of all patients with original medical management will have an aneurysm, further dissection, or surgical requirement within 5 years [17].

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Beta-blockers are the cornerstone of therapy as they affect both BP and contractility and are recommended even for patients with well-controlled BP. Ideal BP control should be <120/80 mmHg. Smoking cessation and risk factor modification for atherosclerotic disease are also key components for chronic management of aortic dissection. Surveillance with CT or MRA should occur at 1, 3, 6, and 12 months. After the first 12 months, imaging can be continued annually. Primary care doctors can oversee this surveillance along with cardiologists or cardiothoracic surgeons as appropriate.

Cardiac Syncope

Syncope is defined as sudden temporary loss of consciousness (LOC) with complete spontaneous recovery. It is very important to obtain a good history and physical exam in order to determine if the patient experienced syncope or if another diagnosis is more likely. If the patient did indeed have a syncopal event, the history and physical exam will help the clinician distinguish between the five types of syncope: cardiac, reflex mediated, neurologic, orthostatic, and psychogenic (see Table 4) [18].

The differential for syncope includes seizures, dizziness, presyncope, drop attacks, vertigo, and near sudden cardiac death events [19]. The history can usually elicit which of these the patient experienced. The input of any witnesses is vital as the patient often does not remember the event or does not remember the entirety of the event. Studies have shown that the elements that distinguish seizure from syncope include disorientation after the event (postictal phase), tongue-biting, frothing at the mouth, and loss of consciousness for more than 5 min. An aura preceding and a headache after the event also suggest seizure [20]. Urinary or fecal incontinence can be seen with either condition but is more common in seizures.

Cardiac syncope is important to distinguish from other causes as it is associated with an increased risk of death from all causes, such as stroke, and from cardiac causes, such as myocardial infarction or arrhythmia. Cardiac syncope is the second most common type of syncope and is seen in about 10–20% of cases. Patients tend to be older, have a cardiac history, and/or have risk factors for cardiac disease such as diabetes and HTN. They may also have palpitations, syncope related to exercise, and/or a family history of sudden cardiac death. They may complain of chest pain or shortness of breath in addition to the syncopal episode. Ventricular tachycardia (VT) is the most common tachyarrhythmia that leads to syncope. Supraventricular tachycardia (SVT) can lead to syncope but this is less common. More often, patients with SVT have less severe symptoms such as lightheadedness, palpitations, and shortness of breath. Bradyarrhythmias such as sick sinus syndrome can also lead to syncope. A massive pulmonary embolism and aortic stenosis are obstructive causes of cardiac syncope. Increased age and male sex, both risk factors for cardiac disease, also suggest a cardiac etiology for syncope.

Risk Factors for Serious Adverse Events After a Syncopal Episode

The San Francisco Syncope Rule (SFSR) is a tool used to determine if a patient has an increased risk of death after a syncopal episode. Systolic blood pressure <90 mmHg, shortness of breath, congestive heart failure, ECG abnormalities, and hematocrit <30 were all predictors of serious outcomes [3S]. Another tool is the Risk stratification Of Syncope in the Emergency department (ROSE) rule. This states that if any of the following seven risks are present, the patient should be considered high risk: BNP > 300 pg/ml, HR <50, hemoglobin <9, positive fecal occult blood, chest pain, ECG with Q waves, or oxygen saturation <94% [21].

Another study looked at death or significant cardiac arrhythmias in the year after a syncopal episode and found that the four most important risk factors were age > = 45, a history of heart failure, a history of ventricular arrhythmia, and an abnormal ECG. Patients with none of these risks had a 4–7% chance of death or a significant

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Table 4 Types of syncope

Name	Situation	Prevalence (%)	Risk of death
Cardiac	Exertional, arrhythmias, palpitations, unprovoked	18	2X increased risk of death from any cause
Reflex mediated	Vasovagal, situational, micturition, defecation, sight of blood	24	None
Neurologic	Steal syndrome, TIAs, neurologic symptoms	10	Increased risk of death
Orthostatic	Dehydration, medication, alcohol, occurs with standing	8	None
Psychogenic	Depression, anxiety, normal exam findings, panic attacks	2	None

All other episodes of syncope are of unknown etiology, 38%

cardiac arrhythmia as opposed to those with three or four of these risks who had a 58–80% chance [21].

History and Physical Exam

Diagnosing and distinguishing between types of syncope, history, and physical exam allow for more accurate diagnosis than any other modality, establishing the cause up to 65% of the time [18]. ECG was next at only 10%.

It is important when taking the history to ask about the patient's position prior to and at the time of the event, last PO intake including fluids, recent exertion, any situational stressors, any new or recently taken medications or drugs, the presence of palpitations or dyspnea, and any family history of cardiac disease and sudden cardiac death. Also ask if the patient has experienced prior episodes of syncope. It is also important to know if the patient has a personal cardiac history including a pacemaker or defibrillator.

The physical exam should include vitals particularly any orthostatic changes and oxygen saturation, cardiac murmurs, arrhythmias, any neurologic changes, or any gastrointestinal blood loss.

Testing

Routine lab testing has little diagnostic value in assessing syncope with <3% of cases having any significant lab abnormalities [21]. It may be reasonable to check glucose, CBC, and BNP in certain patients.

Carotid massage can be used to check for neurally mediated carotid sinus hypersensitivity in patients over age 40 only after ruling out the presence of bruits. This test should not be performed in patients with a history of transient ischemic attack (TIA), recent stroke, or neurologic findings on exam. The test is positive if the patient experiences a pause in heart rate for >3 s or whose systolic BP drops by more than 50 mmHg. The test should be done in the supine and upright positions [20]. While this is mentioned in most texts, it is not often done in practice.

ECG should be ordered for patients where cardiac syncope is suspected. The ECG can establish the diagnosis in 5–10% of cases of syncope. One should look for QT prolongation, delta waves, and short PR interval which suggest Wolff-Parkinson-White (WPW) syndrome, bundle branch block (BBB), and particularly right BBB with ST elevation which is seen in Brugada syndrome. One should also look for ST elevations suggestive of myocardial infarction, bradycardia, second- or third-degree atrioventricular (AV) node block, SVT, or VT. Any abnormality in the ECG should raise the concern for a cardiac cause of syncope and increased mortality [20].

Telemetry is often ordered for patients who present with syncope but does not frequently help identify the cause. Holter monitoring and more recently loop monitoring may be useful in cases of suspected arrhythmia. These allow for longer periods of monitoring with implantable

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loop recorders being able to monitor patients for more than 12 months. Symptoms attributable to arrhythmias can be found with loop recorders in 50–85% of cases [21].

Stress testing and cardiac catheterization should only be used in cases where myocardial ischemia is highly suspected.

Echocardiography is useful to evaluate for structural cardiac abnormalities. It is also useful for determining left ventricular ejection fraction (EF) as an EF <35% is an indication for an implantable cardioverter-defibrillator (ICD). These patients are at high risk for arrhythmias and sudden cardiac death. In these patients, syncope is an ominous sign. Echocardiography is also useful in establishing aortic stenosis as the cause of syncope. This should be suspected in older adults presenting with syncope during exertion.

Electrophysiologic (EP) testing can be useful in establishing the diagnosis for patients suspected of having sick sinus syndrome, heart block, ventricular tachycardia (VT), or supraventricular tachycardia (SVT). Those patients with structural heart abnormalities, ECG abnormalities, a clinical history that suggests arrhythmia, or a family history of sudden death should undergo EP testing.

Management

Management of cardiac syncope depends on the underlying cause. If the cause is ischemic, patients should receive optimal medical management along with surgical interventions as needed. Most arrhythmias will require ICD implantation. Patients with sick sinus syndrome and AV node block can be treated with pacemakers. WPW can be treated with catheter ablation therapy.

Sudden Cardiac Death

Sudden cardiac death (SCD) affects between 300,000 and 500,000 people in the United States annually. SCD is usually caused by VT decompensating to ventricular fibrillation (VF) though it may also result from heart failure, bradyarrhythmias, heart block, or pulmonary emboli. SCD is responsible for more deaths annually in the United States than stroke, lung cancer, and breast cancer combined. Worldwide, it is responsible for 50% of overall cardiac deaths [22]. It is the most common presenting sign of coronary artery disease. Risks for SCD include decreased left ventricular EF, acute MI, prior MI, prior ventricular arrhythmia, and congestive heart failure.

Seventy-five percent of cases occur in men with a fourfold to sevenfold higher risk of SCD in men than women <65 years of age. After age 65, the ratio of SCD in men to women is 2:1 or less [22]. Pre-menopausal women have some cardioprotection that decreases their risk of SCD and cardiac disease. However, in women over age 40, coronary artery disease is the most common cause of SCD. Further, women with SCD are less likely to have severely reduced left ventricular ejection fraction or known heart disease which makes it that much harder to establish a risk profile for women.

Studies show that more than 50% of people with SCA had warning symptoms before the event; however, they often went unrecognized or minimized. The most common symptoms were chest pain and dyspnea. Women experienced dyspnea more than chest pain.

Risk factors for SCD (or SCA) are the same as for coronary heart disease (CHD): smoking, obesity, inactivity, dyslipidemia, diabetes, hypertension, and family history of CHD [23].

Primary Prevention

Given that the first arrhythmic event is usually fatal in SCD (or perhaps more appropriately, sudden cardiac arrest (SCA)), it is critical to try to identify people who are at high risk for these events and intervene early. People with known cardiac disease and ejection fraction (EF) < 30–40% are known to be at very high risk for SCD. An EF < 30% is the biggest independent predictor for SCD, and reduced EF predicts SCD in both ischemic and nonischemic dilated cardiomyopathies. The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) published guidelines

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recommending ICD implantation in people with EF less than 30–35% with heart failure [24]. Therefore, it is critical that any patient with known cardiac disease have an evaluation for ejection fraction. Patients with low functional capacity who don't have a reasonable expectation to live more than 1 year are not candidates for ICDs.

Secondary Prevention

Three studies have shown that ICDs decrease mortality in patients with aborted SCD, VT, or VF. Therefore, any patient with a history of VT, VF, SCA, or aborted SCD should be evaluated for possible ICD implantation. VT or VF that occur within 48 h of an MI do not need to be evaluated for ICD placement.

Hypertrophic Cardiomyopathy

Definition

Hypertrophic cardiomyopathy (HCM) is defined as LV hypertrophy associated with nondilated ventricles that is not caused by cardiac or other systemic illness. HCM affects approximately 600,000 people in the United States. Most of those have no symptoms and most have a normal life expectancy. Those that do die from SCD suffer from ventricular tachyarrhythmias. This occurs most often in asymptomatic patients younger than 35. The other two serious complications of HCM are atrial fibrillation (AF) and heart failure with dyspnea.

The complications of HCM are caused by left ventricular outflow tract (LVOT) obstruction, arrhythmias, myocardial ischemia, diastolic dysfunction, and mitral regurgitation [25]. It is critical to establish whether LVOT obstruction is present as management strategies are based largely on this complication.

Diagnosis

The diagnosis of HCM is made by transthoracic echocardiography (TTE) and more recently, cardiac MRI. Once HCM is diagnosed, first-degree relatives should be screened with TTE. Patients with HCM can undergo genetic testing. If a patient screens positive for one of the genetic markers of HCM, first-degree relatives can be screened with genetic testing as well.

If a patient is diagnosed with HCM, ECG, and Holter monitoring should be done to look for any tachyarrhythmias. This should be repeated annually or whenever the patient has worsening symptoms of HCM [25].

Children of patients with HCM should be screened annually with TTE starting at age 12 or earlier if puberty or growth spurt begins before age 12. Children in intense competitive sports should also be screened earlier. Adult relatives can be surveyed every 5 years with TTE.

Management

Providers should aggressively manage patients with asymptomatic HCM by evaluating them for other risk factors for cardiovascular disease as these may contribute to complications of HCM. These patients should not participate in strenuous activities or competitive sports. Patients with resting or provoked LVOT obstruction should not be given high-dose diuretics or pure vasodilators as these are harmful. Beta-blockers should be used as first-line medications for symptoms of dyspnea and angina. If patients cannot tolerate these, verapamil can be used. Disopyramide (Norpace) can be added to a beta-blocker or verapamil if symptoms cannot be controlled; however, it should not be used alone. Dihydropyridine calcium channel blockers such as amlodipine (Norvasc) should not be used in patients with HCM who have LVOT obstruction. ACE inhibitors have not been shown to be useful or harmful in the treatment of symptoms of HCM. Beta-blockers can be used in children but watch for side effects such as depression or difficulty in school.

Surgical interventions such as septal reduction or alcohol septal ablation should only be considered in cases of refractory LVOT obstruction and symptoms that interfere with daily living despite optimal medical management. These should only be performed at experienced centers.

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Implantable cardiac defibrillators (ICDs) have been shown to decrease mortality in patients with HCM and tachyarrhythmias. Patients with HCM should receive risk stratification for SCD to determine if an ICD if appropriate. These include prior personal cardiac arrest, history of VF, sustained VT, sudden cardiac arrest (SCA) (recurrence is 10% per year), family history of SCD, unexplained syncope, documented nonsustained VT, or LV thickness > = 30 mm [25]. An ICD can be implanted in children as well who have any of these high-risk factors.

Patients with HCM, regardless of symptoms, should not participate in intense or competitive sports. One third of all SCD in young athletes are due to HCM. Low-intensity aerobic exercise is recommended.

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Venous Thromboembolism

85

Lawrence Gibbs, Josiah Moulton, and Vincent Tichenor

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Introduction

DVT and PE have shared pathophysiology and together, along with superficial venous thrombosis, comprise the spectrum of venous thromboembolism (VTE). PE is the most serious of these, causing up to 10% of deaths in the hospital setting, and represents the most common preventable cause of death in patients with misdiagnosed

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or improperly treated PE or DVT [1]. Even though the number of in-hospital deaths due to PE has decreased in the US, up to 30% of patients still die within the first year of diagnosis [2]. It is critical to maintain a high clinical suspicion in patients at risk of VTE and apply current diagnostic tools appropriately in order to initiate prompt therapy.

Pathophysiology

The major theory describing the pathogenesis of VTE is a triad derived from the extensive research of Virchow almost 100 years after his passing. This theory states that thrombosis occurs due to a combination of endothelial injury, hemodynamic changes (such as stasis or turbulence), and changes in the balance or properties of blood components involved in the coagulation cascade (i.e., inherited or acquired states of hypercoagulability) [3]. The role of inflammation is apparent by the increased frequency of DVT and PE formation in chronic inflammatory conditions such as inflammatory bowel diseases and systemic vasculitis [4]. C-reactive protein elevation has been linked to increased VTE risk. In the Atherosclerosis Risk in Communities (ARIC) study, an elevated C-reactive protein above the 90th percentile was associated with a 76% increased risk of VTE formation compared to lower percentiles [4]. Endothelial injury and stasis also increase VTE risk via increasing coagulation factors and preventing adequate mixing of anti-clotting factors, respectively [4, 5]. Local injury from indwelling devices, such as pacemaker leads or long-term indwelling central venous catheters, also increases upper extremity DVT formation [5].

Inherited and acquired thrombophilias affecting anticoagulant or pro-coagulant pathways lead to hypercoagulopathy [6]. Common inherited disorders include factor V Leiden mutation, which causes resistance to degradation by activated protein C, G2021A mutation, and deficiencies in proteins C and S, and antithrombin III. Hyperhomocysteinemia spans both categories, as it involves inheriting a defective enzyme, but is acquired through dietary folate, B6 and B12 deficiency [7]. Antiphospholipid antibody syndrome is an acquired autoimmune disorder characterized by abnormal levels of lupus anticoagulant, anti-β-2 glycoprotein-1, and anticardiolipin antibodies that increase the risk of recurrent VTE [8].

Inherited coagulopathies are among the rare, but significant risk factors for development of VTE, particularly in younger populations. However, thrombophilia testing remains controversial as absolute VTE risk is only mildly affected by these disorders, and currently available thrombophilia tests are insufficient to identify inherited risks of VTE [8]. The majority of patients with VTE should not be tested for thrombophilia, and most patients with inherited thrombophilia can accurately be identified based on the patient's personal and family history of VTE and not require testing [8]. Of those risks mentioned, family history of an unprovoked VTE in a first-degree relative, especially under age 50, may be more important in terms of counseling patients on their inherent risk (i.e., during pregnancy) than specific testing results [8, 9].

Epidemiology

Only myocardial infarction and stroke are more common in terms of cardiovascular disease than VTE [1]. The annual frequency of first-time VTE in adults is 1–2:1000 (rising to 1:200 in those over age 70), and if left untreated, the 30-day mortality rate for a first-time DVT is 5% and as high as 33% for those with a PE [9, 10]. The incidence of VTE increased significantly from 2001 to 2009 and may in part reflect improvement in imaging quality and increased use of diagnostic studies [9].

Approximately 33% of patients with VTE have recurrence within the following 10 years [10]. Predictors of recurrence include prior VTE, increased age, increased BMI, male gender, active cancer, and leg paresis among others. VTE accounts for approximately 1% of hospital admissions in the USA annually, and two-thirds of VTE cases occur in patients who have been hospitalized within the past 90 days [7]. Hospitalization, illness with

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resulting inflammation, recent surgery, and chemotherapy can all increase the risk of VTE by up to 100-fold [6, 7].

Men over age 45 are typically higher risk than similarly aged women, but women are 2–4 times higher risk during pregnancy, and the risk to postpartum women is as much as 5 times that during pregnancy [9]. In terms of race, the age-adjusted VTE incidence for those of European descent appears to be 104–183 per 100,000. Most data indicate the risk for African-Americans is slightly higher than this, but the risk may differ based on the region in the USA. The risks in Asian and Native Americans are estimated to be much lower [5, 9]. Among the highest incidence of VTE in the community include patients with a central venous catheter or transvenous pacemaker (9%) nursing home patients (10%) and active cancer (20%) [9]. Cancer may increase the risk of VTE in various ways such as through the elaboration of pro-inflammatory products which activate the coagulation cascade or through a tumor compressing vessels which causes stasis. The incidence of VTE during the first 6 months after a cancer diagnosis is 12.4 per 1,000 [11].

Modifiable risk factors for VTE include obesity, hypertension, tobacco use, dyslipidemia, diabetes, diet, stress, hormone replacement therapy, and contraceptive use. Patients with a BMI >30 have a two- to threefold higher risk for VTE, and may be related to impaired venous return or increased coagulation and inflammation [7]. Regarding contraceptive use, while the levonorgestrel intrauterine device imparts no additional risk, first- and third-generation oral contraceptives are at higher risk than second-generation contraceptives, and the depo-medroxyprogesterone injection carries a threefold increased risk for VTE from baseline [9]. Table 1 includes further risk factors for VTE.

The most significant sequelae of VTE are venous stasis syndrome, venous ulcers, and chronic thromboembolic pulmonary hypertension. The 20-year incidence of venous stasis syndrome after VTE and proximal DVT is close to 25% and 40%, respectively, while that of venous ulceration is 3.7% [6].

Table 1 Risk factors for venous thromboembolism

Strong risk factors (odds ratio ≥ 10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Moderate risk factors (odds ratio 2–9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy/Postpartum
Previous venous thromboembolism
Thrombophilia
Weak risk factors (odds ratio ≤ 2)
Bed rest >3 days
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy/Antepartum
Varicose veins

Used with permission from Anderson FA, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107(23):I9–I16

Diagnosis

Evaluating the history, signs, symptoms, and the individual's risk factors for VTE is essential for the diagnosis of DVT and PE (see Table 1). Patients with symptomatic DVT classically present with unilateral calf or thigh swelling, warmth, and tenderness. However, peripheral arterial disease (PAD), trauma, infection, and compartment syndrome may share these features. Likewise, patients suspicious for PE commonly present with one or more symptoms of chest pain, tachypnea, tachycardia, dyspnea, cough, and syncope. Concurrent DVT symptoms may also be present in those with suspected PE. Congestive heart failure (CHF), acute coronary syndrome (ACS), and chronic obstructive pulmonary

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disease (COPD) share similar signs and symptoms as PE and may confound the diagnosis [12].

Clinical Approach

Because none of the signs and symptoms of DVT or PE are specific, clinical probability assessment is an essential component in the diagnosis. Clinical prediction rules that incorporate signs, symptoms, and patient risk factors are frequently utilized to categorize patients as low, moderate, or high probability of having VTE [13]. Numerous guidelines recommend the use of validated clinical prediction rules to assess pretest probability of VTE to guide diagnostic decision-making [12, 14, 15].

A variety of formal scoring systems have been developed and validated to assist in stratifying patients with suspected DVT or PE [12]. Wells' DVT criteria is frequently used for DVT assessment and assigns a pretest probability category based on risk factor scoring. Patients are determined to be low (≤0), moderate (1–2), or high risk (≥3) for DVT based on their scores [15]. Wells' DVT criteria are shown in Table 2. Meanwhile, Wells' PE criteria [16] and the modified Geneva criteria [17] have similar predictive value and assist providers in determining pretest probability for PE [14]. Similar to the Wells' DVT criteria, the physician assigns points for different clinical criteria to obtain a pretest probability score. For the Wells' PE criteria, a patient's pretest probability is considered low for scores less than 2, moderate for scores between 2 and 6, and high for scores greater than 6. Wells' and the modified Geneva criteria are shown in Table 3. Simpler, two-tier/dichotomous versions of the Wells' and Geneva scores do exist (e.g., low risk vs high risk), but caution is advised since prospective validation of these models is still needed [14]. Also, though some suggest a simple gestalt approach to pretest probability, determination based on experience is often inaccurate and should be used cautiously [12]. Pretest probability for DVT or PE, along with test availability and risk, should guide subsequent D-dimer and diagnostic imaging (see algorithm) [18]. For those patients at low risk for PE determined by Wells' criteria, the Pulmonary Embolism Rule Out Criteria (PERC rule) can be used to effectively rule out PE (<1% of low-risk patients who are PERC negative will develop PE within 30 days) [18, 19].

Table 2 Wells' DVT Criteria

Variable	Points
Active cancer (treatment ongoing or within previous 6 months of palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for >3 days or major surgery within 4 weeks	1
Localized tenderness alone the distribution of the deep venous system	1
Entire lee swollen	1
Calf swelling by >3 cm when compared with the asymptomatic leg	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (not varicose)	1
Alternative diagnosis as likely or more likely than that of deep-vein thrombosis	-2
Analysis	
Probability of DVT is low	≤0
Probability of DVT is moderate	1 or 2
Probability of DVT is high	≥3

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D-Dimer Testing

D-dimers are a byproduct of fibrinolysis formed by the degradation of fibrin within a clot and are acutely elevated in VTE [12]. The use of D-dimer testing with diagnostic algorithms that include pretest probability assessments can effectively exclude VTE in roughly 30% of patients suspected of having DVT or PE [2, 20]. Current assays are fast, readily available, and highly sensitive for DVT (over 93%) and PE (over 95%), but not nearly as specific [14]. False positives can be seen in patients with malignancy, infection, recent surgery or trauma, and pregnancy [13]. It is worth noting that since D-dimer levels increase naturally with age, for patients 50 years or older, using an

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Table 3 PE clinical decision rules

Wells rule variable [16]	Points	Revised Geneva score variable [17]	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of deep veins)	3	Age > 65	1
An alternative diagnosis is less likely than PE	3	Previous DVT or PE	3
Heart rate > 100	1.5	Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month	2
Immobilization or surgery in the previous 4 weeks	1.5	Active malignant condition (solid or hematologic, currently active or considered cured <1 year)	2
Previous DVT/PE	1.5	Unilateral lower-limb pain	3
Hemoptysis	1	Hemoptysis	2
Malignancy (on treatment, treated in the last 6 months or palliative)	1	Heart rate 75–94 beats min^{-1}	3
		Heart rate > 94 beats min^{-1}	5
		Pain on lower – limb deep venous palpation and unilateral edema	4
Clinical probability		*Clinical probability*	
Low	<2 total	Low	0–3 total
Intermediate	2–6 total	Intermediate	4–10 total
High	>6 total	High	>10 total

Reprinted from Klok FA, Kruisman E, et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. J Thromb Haemost. 2008;6(1): 40–44

age-adjusted D-dimer, defined as a patient's age multiplied by 10, may be more accurate at ruling out VTE than using the typical fixed D-dimer cutoff of 500 ug/L [20, 21]. This approach appears very useful in ruling out PE, but prospective validation of its use to rule out DVT is currently ongoing [2].

Compression Ultrasound (CUS)

Widely available and noninvasive, CUS is the imaging procedure of choice for the diagnosis of DVT, with a sensitivity and specificity of 95% and 98%, respectively, when performed by a well-trained operator [14]. Inability to compress a vein with the transducer is diagnostic for DVT, while signs of distention, decreased flow, and abnormal Doppler signal support the diagnosis [13]. In patients with moderate to high pretest probability of DVT, negative CUS alone, especially if just proximal vessels were tested, cannot exclude the diagnosis of DVT [14]. Repeat CUS 1 week later is recommended for this group [13]. Some limitations include decreased reliability in detecting calf and upper extremity thrombi or poorer detection of thrombi isolated to the pelvis and difficulty distinguishing between old and new clots [12].

Venography

Once considered the gold standard for DVT detection, venography involves injecting contrast into the venous system to assess for filling defects or collateral flow. The PIOPED II trial demonstrated CT venography to be diagnostically equivalent at identifying DVT compared to CUS at the risk of higher contrast and radiation exposure [22]. Currently, venography is reserved for times when noninvasive tests cannot be performed or when noninvasive tests yield results counter to clinical suspicion [12].

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Computed Tomographic Pulmonary Angiography (CTPA)

Multi-detector CT angiography has replaced conventional pulmonary angiography as the reference standard for diagnosing PE with high sensitivity and specificity of up to 100% and 97%, respectively [23]. Not only does it meet or exceed pulmonary angiography in ability to rule out PE, but it also generates diagnostic information that may suggest alternative or additional diagnoses [23]. Additionally, the PIOPED II trial showed that for those with high or intermediate pretest probability and positive CTPA results or those with low pretest probability and normal CTPA results, predictive values in the mid-90s were achieved [22]. Due to increased ionizing radiation and contrast exposure, consider ventilation-perfusion (V/Q) scanning for pregnant women, obese patients, or those with compromised renal function [12, 18].

Ventilation-Perfusion (V/Q) Scanning and V/Q SPECT

Ventilation-perfusion (V/Q) lung scans are reported as low, intermediate, or high likelihood for the presence of PE. A normal scan effectively excludes PE (negative predictive value of 100%) [23], while high pretest probability and a high-probability V/Q scan have a positive predictive value of 96% [18]. Unfortunately, approximately two-thirds of scans are not definitive and fall in the intermediate/non-diagnostic range [18]. As with CTPA, results discordant with pretest probability require further workup. Advances in V/Q single-photon emission CT (SPECT) have increased its sensitivity and specificity while limiting non-diagnostic results, which plague typical planar V/Q scans [18]. Though not available in all centers, its interobserver variability and diagnostic accuracy (both sensitivity and specificity of 96–97%) are superior to planar V/Q scans [24]. A single systematic review and meta-analysis also showed V/Q SPECT to be equivalent to CTPA in terms of diagnostic accuracy while allowing less radiation exposure but at a cost approximately twice that of CTPA [25].

Other Diagnostic Testing

Pulmonary angiography may still be considered in select cases where clinical suspicion for PE remains high despite negative prior testing, but it is more invasive and requires higher contrast exposure than CTPA [12]. Those with normal angiography results have a 3-month VTE incidence less than 2% with 0.3% incidence of fatal PE [26]. Meanwhile, the PIOPED III trial did show magnetic resonance angiography and venography (MRA and MRV) to have good sensitivity and specificity at detecting PE, but their high percentage of technically inadequate results currently do not support routine use [18, 27]. Additionally, tests like a chest x-ray showing pleural infiltrates, or engorged central pulmonary artery vasculature with a paucity of peripheral vessels, or an electrocardiogram showing right bundle branch block with the a S1Q3T3 pattern may increase suspicion for PE but are not specific [12] (Fig. 1).

Management

Management of VTE centers on initial stabilization of the patient, selection of anticoagulation therapy, and determining treatment duration. Providers may start empiric pharmacological treatment in high-risk patients (based on pretest probability) while undergoing testing, and delay treatment until testing is finished for low-risk patients, but there is insufficient data to support that administering anticoagulation prior to imaging improves morbidity or mortality [18]. A distal DVT is less likely to embolize than a proximal DVT, and a DVT that does not extend within a period of 2 weeks is unlikely to extend into the proximal veins. Therefore, for acute isolated distal DVT in a patient without severe symptoms or risk factors (i.e., positive D-Dimer, extensive thrombosis, thrombus near proximal veins,

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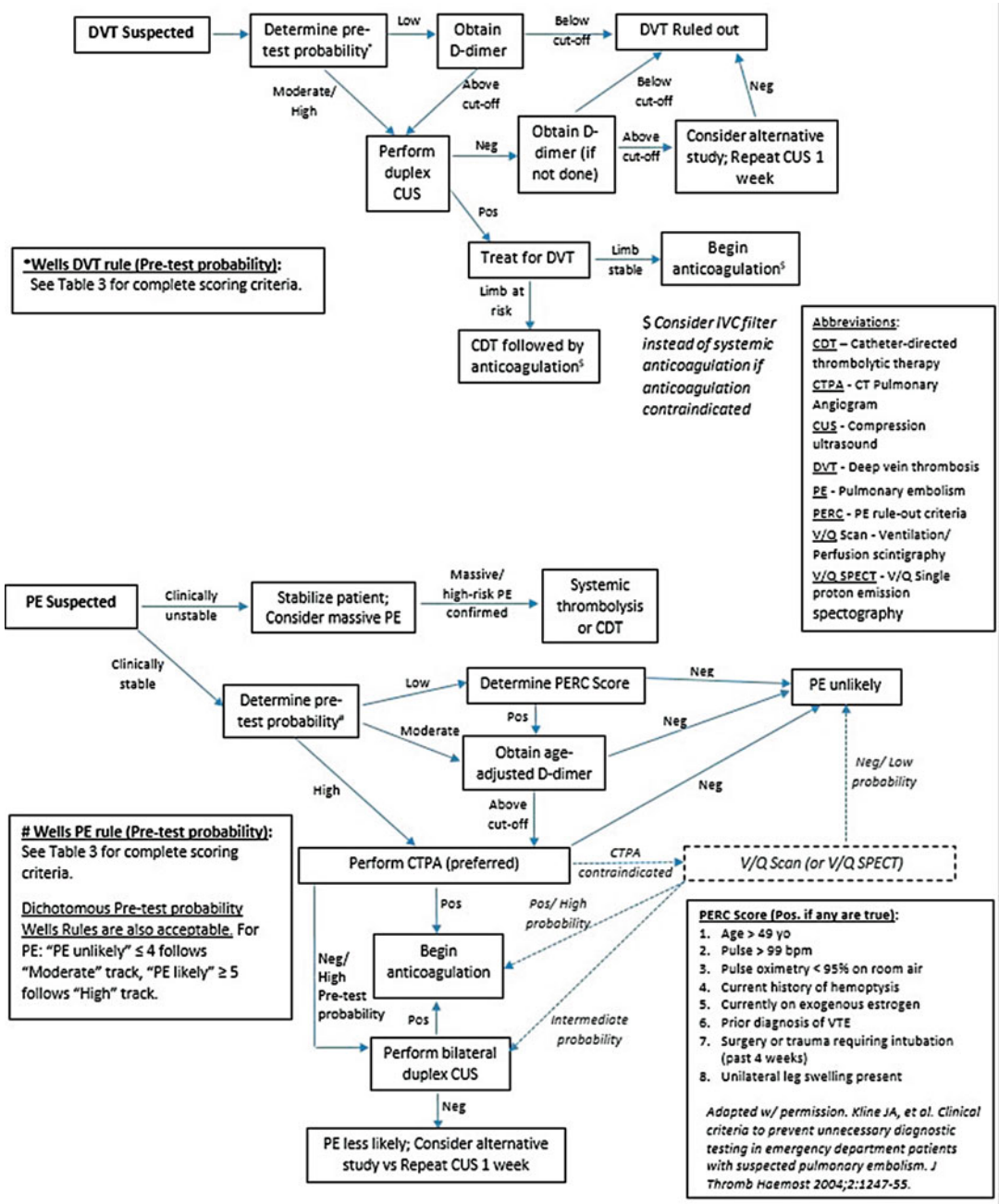


Fig. 1 Diagnostic algorithms for DVT (top) and PE (bottom) [14, 15, 18]

absence of reversible provoking factor, prior VTE, or inpatient status), the physician may delay anticoagulation and repeat imaging of the deep veins in 2 weeks [28]. Similarly, for asymptomatic patients with small, sub-segmental PEs and no DVT, recent guidelines suggest clinical surveillance over anticoagulation [28].

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Initial Management

Given the variation of severity in patients who present with PE, the provider must ensure hemodynamic stability. For patients who are stable (such as with an isolated single DVT of the leg or segmental PE with hemodynamic stability), initial therapy can be initiated with a goal to move to long-term anticoagulation. However, in more critical situations, such as acute massive PE, PE in a patient who is hypotensive, PE with significant right ventricular strain (i.e., cardiac biomarker elevations or right ventricular strain shown on echocardiogram or CTPA), or extensive acute proximal DVT, early thrombolysis may be needed in addition to respiratory and hemodynamic support [28]. Early lysis of the thrombus and reducing post-thrombotic morbidity [28, 29] may be achieved through venous infusion of a thrombolytic agent (systemic thrombolysis) or delivery into the thrombus via catheter-direct thrombolysis (CDT). Current guidelines still prefer systemic thrombolysis over CDT [28] as most data show that systemic thrombolysis and CDT have similar effectiveness [30], but the resources required for systemic thrombolysis are more widely available. However, in certain circumstances (such as severe PE or failure of systemic thrombolysis), CDT may be more appropriate assuming the resources and expertise to perform the procedure are available [2]. Emerging techniques, such as pharmacomechanical thrombectomy (PMT), are still being developed, and no specific guidelines yet exist regarding them. Once the patient is stable, the treatment focus may be shifted toward anticoagulation, which is broadly the same in patients with PE or DVT [13, 28].

Anticoagulation has traditionally been accomplished with initial treatment with unfractionated heparin (UH) or low-molecular-weight heparin (LMWH) to achieve immediate anticoagulation, along with a vitamin K antagonist (VKA, typically warfarin) to achieve long-term anticoagulation [31]. Initial treatment with subcutaneous UH, LMWH, or fondaparinux is required to allow time for the VKA to begin to work [32], after which frequent testing via PT/INR is required to ensure the VKA is dosed within an effective range [28, 33].

UH has long been utilized in the initial treatment of VTE and when given intravenously (IV), is dosed via a nomogram based on periodic monitoring of the patient's activated partial thromboplastin time (aPTT) [34]. IV UH is preferred in patients with PE who will likely undergo thrombolysis (due to its shorter action and easier reversibility), those with impaired subcutaneous absorption, or those with increased bleeding risk [31]. UH carries the risk of heparin-induced thrombocytopenia (HIT), hemorrhage, and anaphylaxis. The risk of hemorrhage increases with age, comorbidities, and previous bleeding. Due to the risk of HIT, patients on heparin should have their platelet count monitored daily. Despite UH's long history of use, LMWH and fondaparinux have become the favored initial treatment for uncomplicated VTE as both have equal efficacy, increased bioavailability, and less frequent dosing when compared to heparin [32].

While the traditional regimen of bridging initial subcutaneous anticoagulation with long-term oral anticoagulation is still a viable method of treatment, evidence has shown that immediate therapy with either rivaroxaban or apixaban can safely replace the traditional regimen, eliminating the need for the use of heparin injections or frequent monitoring required by VKAs [28, 35, 36]. Direct oral anticoagulants (DOACs) are now preferred as first-line anticoagulant therapy in most patients [28, 33, 37] due to their rapid onset of action, predictable pharmacokinetic profile, and comparative effectiveness for treating VTE compared to LMWH and warfarin [2]. An exception to this management strategy is VTE associated with malignancy where most guidelines recommend that the patient be anticoagulated with LMWH for the duration of their treatment [28, 31, 37]. However, evidence from recent randomized control trials (Hokusai-VTE Cancer [38], SELECT-D [39], and CARAVAGGIO [40]) shows that DOACs (edoxaban, rivaroxaban, and apixaban) are non-inferior to LMWH for treatment of VTE in patients with cancer without significant increased bleeding risk (highest risk found in those with

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gastrointestinal malignancies) and could be an option for this group of patients.

Outpatient initial management may be appropriate in low-risk patients. Criteria for outpatient therapy include patients with good cardiorespiratory reserve, no excessive bleeding risks, a creatinine clearance greater than 30 mL/min, and ability to safely self-administer the medication [28, 33]. Well-validated clinical scores, like the Pulmonary Embolism Severity Index (PESI) and simplified-PESI (sPESI), can also be used to provide objective measures of a patient's appropriateness for initial outpatient management and hospital discharge [33]. Each provides reliable identification of patients at low 30-day mortality risk using baseline indicators of PE severity and the individual's comorbidities and potentially aggravating conditions. For the sPESI, a high-risk patient meets at least one of the following requirements: age over 80 years old, history of cancer, chronic cardiopulmonary disease (i.e., chronic obstructive pulmonary disease or congestive heart failure), pulse over 100 beats per minute, systolic blood pressure under 100 mmHg, or oxygen saturation less than 90% [33]. See Table 4 for a summary of treatment options.

Long-Term Anticoagulation

Goals of long-term anticoagulation therapy include preventing clot propagation, preventing possible PE (primary or subsequent), and minimizing complications. Resolution of an existing clot is not a direct goal of anticoagulation therapy [13, 28]. Recommended duration of therapy varies based on clinical circumstances, with a minimum treatment length of 3 months [28, 31]. Generally (with the exception of UH), the initial form of anticoagulation can be continued as the patient's long-term anticoagulation agent. However, given that LMWH and fondaparinux are both administered subcutaneously, it is typically favored to transition to an oral anticoagulant.

VKAs, LMWH, fondaparinux, and direct oral anticoagulants (DOACs) may be used to provide long-term anticoagulation [31]. The longest used agent is warfarin, a VKA. Warfarin was previously preferred due to time-proven efficacy, oral administration, reversibility, and low cost. However, periodic lab testing, narrow therapeutic window, need for dosage adjustments, and its interactions with many drugs and foods may limit its use [31]. When using warfarin for long-term anticoagulation, initial therapy should be continued for a minimum of 5 days and at least 24 h after the patient's international normalized ratio (INR) is above 2.0. The initial subcutaneous or IV therapy provides adequate anticoagulation, while the vitamin K-dependent clotting factors are depleted. The goal INR value for treatment is 2.5, with an acceptable range of 2.0–3.0 [28, 31]. Various tables and algorithms are available to guide warfarin dosing based on INR testing. One such validated protocol suggests monthly INR testing for patients within their therapeutic window, and weekly testing for those outside of this range, which is supported by groups like the American Society of Hematology [37].

LMWH is also a viable option with similar efficacy and risk profile when compared to warfarin for long-term anticoagulation [41]. LMWH is advantageous due to its ease of dosing, wide therapeutic window, no need to monitor, and fewer drug/food interactions compared to warfarin. However, it is also more expensive than warfarin, more difficult to reverse, requires subcutaneous dosing, and carries a risk of drug-induced osteoporosis. LMWH is preferred in patients with malignancy for long-term treatment by most guidelines [28, 37]. Fondaparinux is a subcutaneous agent that is similar to LMWH in use and may also be used in long-term treatment [31, 37].

DOACs are quickly becoming the treatment of choice for long-term anticoagulation as evidence supports their effectiveness compared to warfarin for long-term therapy [35, 36, 42]. Also, most current guidelines recommend these as first-line treatment for VTE that is not associated with malignancy due to continued evidence demonstrating their safety and efficacy [28]. Compared with LMWH treatment followed by long-term VKA treatment, DOACs are non-inferior for recurrent VTE and have a lower risk of major bleeding [43]. Meta-analyses have also

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Table 4 VTE treatment options [2, 28, 31, 33, 43]

Parenteral anticoagulants								
Agent	**Mechanism**	**Dosing**	**Half-life**	**Metabolism**	**Antidote**	**Monitoring**	**Miscellaneous**	
Heparin	Binds antithrombin	IV: 80 U/kg bolus, then 18 u/kg/h (adjust w/ aPTT) SC: 333 U/kg, then 250 u/kg q12 h	90 min	Depolymerization	Protamine	aPTT (1.5–2.0 × Normal)		
LMWH (enoxaparin)	Binds antithrombin	SC: 1 mg/kg BID (daily if CrCl<30); 1.5 mg/kg daily (BMI < 30)	3–4 h	Depolymerization, desulphation	Protamine	None required	Max dose 180 mg/day	
LMWH (Dalteparin)	Binds antithrombin	SC: 100 U/kg q12h or 200 U/kg once daily	3–4 h	Depolymerization, desulphation	Protamine	Anti-Xa levels if CrCl <30 mL/mm	Max dose 18,000 U/day	
Fondaparinux	Indirect factor Xa inhibitor	SC: 5.0 mg daily (<50 kg); 7.5 mg daily (50–100 kg); 10 mg daily (>100 kg)	17–21 h	Insignificant	None	None required	CrCl 30–50 mL/min, use with caution; if CrCl<30 mL/min: use alternative agent.	
Oral anticoagulants								
Agent	**Mechanism**	**Dosing**	**Half-life**	**Drug interactions**	**Antidote**	**Monitoring**	**Parenteral anticoagulation**	**Miscellaneous**
Vitamin K antagonist (warfarin)	Indirect thrombin inhibition	Initial dose 5-10 mg daily, changes based on INR	36 h	CYP2C9, CYP1A2, CYP3A4	Vitamin K	INR (2.0–3.0)	Initially required, 5–10 days	Ok in patients with CrCl<30 mL/min and those on potent P-glycoprotein inhibitors or CYP450 3A4 inhibitors or inducers.

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Dabigatran[a]	Direct thrombin inhibitor	150 mg BID; CrCl 30–50 or age > 75 yo: 110 mg BID; CrCl 15–30: 75 mg BID	14–17 h	P-glycoprotein inducers/inhibitors	Idarucizumab	None required	Initially required, 5–10 days	CrCl <15, not defined
Apixaban[a,b]	Factor Xa inhibitor	10 mg BID for 7 days, then 5 mg BID. 2.5 mg BID if treating beyond 6 mos	8–12 h	CYP3A4/5. P-glycoprotein inducers/inhibitors	Andexanet alfa	None required	None required	2.5 mg BID if at least 1 criterion is met: Serum Cr ≥ 1.5 mgdL, age 80 yo, weight 60 kg or less
Rivaroxaban[a,b]	Factor Xa inhibitor	15 mg BID for 21 days, then 20 mg daily (15 mg daily if CrCl 15–50). 10 mg daily if treating beyond	7–11 h	CYP3A4, CYP2J2, P-glycoprotein inducers/inhibitors	Andexanet alfa	None required	None required	If CrCl <30, consider alternative agent.
Edoxaban[a,b]	Factor Xa inhibitor	30 mg (if ≤60 kg, or CrCl 15–50) or 60 mg daily (if >60 kg & CrCl >50)	6–11 h	P-glycoprotein inducers/inhibitors	None	None required	Initially required, 5–10 days	CrCl <15, consider alternative agent

aPTT activated partial thromboplastin time, *BID* twice daily, *BMI* body mass index, *CrCl* Creatinine clearance (mL/min), *INR* international normalized ratio, *IV* intravenous, *SC* subcutaneous

[a]Limited data in those with creatinine clearance (CrCl) less than 30, antiphospholipid syndrome, heparin-induced thrombocytopenia, BMI >40 kg/m^2, or VTE at unusual sites

[b]Generally avoided if concurrent use of azole antimycotics (e.g., ketoconazole), certain protease inhibitors (e.g., ritonavir), and antiepileptic drugs (e.g., carbamazepine & phenytoin). Note: information on conversion to and from DOACs and warfarin can be found in reference [31] (eTable A). https://www.aafp.org/afp/2017/0301/hi-res/afp20170301p295-ta.gif (Accessed March 1, 2020)

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shown good tolerability in elderly patients [44]. In addition, as mentioned above, evidence for DOACs effectiveness and safety for treatment of VTE in patients with cancer is growing [38–40].

Length of Therapy and Extended Anticoagulation

The length of therapy for anticoagulation depends upon the clinical picture surrounding the VTE with the standard length of anticoagulation therapy being at least 3 months. Anticoagulation that lasts for 3–6 months is considered "long-term anticoagulation," whereas anticoagulation extending beyond 3–6 months without a scheduled stop date is considered "extended anticoagulation" [2]. The decision to extend therapy beyond 3 months is based on balancing the benefits of treatment (i.e., reduction in VTE recurrence based on patient risk factors) and the risks of treatment (i.e., increased bleeding) [2, 31]. For provoked VTE (i.e., a VTE with a known cause such as surgery or non-surgical risk factors), whether a DVT of the leg or PE, anticoagulation can be stopped after 3 months as long as there is no recurrence. For those with unprovoked VTE, the decision to extend anticoagulation beyond 3 months should be based on their bleeding risk. If they have a low or moderate bleeding risk, extended therapy (no scheduled stop date) is preferred. If they have a high bleeding risk, 3 months of therapy is preferred [28, 33]. Reasons to treat for longer than 6 months include those with a first or second unprovoked PE or proximal DVT of the leg, patients with active cancer and VTE, or those with genetic thrombophilias, so long as they are at low or moderate risk of bleeding [28, 31]. Prediction models for quantifying bleeding risk like the HAS-BLED or VTE-BLEED scores can be used to help the clinician stratify bleeding risk [33]. For extended therapy with DOACs beyond 6 months, current guidelines recommend the use of the prophylactic doses of apixaban and rivaroxaban (2.5 mg twice per day and 10 mg daily, respectively) [2, 33].

Additional Therapy

Daily low-dose aspirin (~100 mg) after the initial anticoagulation treatment period may be considered, particularly in patients on extended anticoagulation who elect to stop anticoagulation [28, 33]. Pooled results of the randomized, multicenter WARFASA and ASPIRE trials showed a 32% reduction in the rate of recurrence of VTE in patients receiving aspirin following anticoagulation therapy [45]. The use of compression stockings can be justified to lessen symptoms of existing acute or chronic post-thrombotic syndrome (PTS), but are not recommended for the use of prevention of PTS [28]. Inferior vena cava (IVC) filters are reserved for those with PE or proximal DVT and a contraindication to or a complication from anticoagulant treatment [28]. They have not been shown to reduce recurrent PE in previously anticoagulated patients who have additional risk factors for recurrence [33].

Prevention

Recognizing those factors that increase one's risk for VTE is essential for prevention. Extended or life-long anticoagulation may be appropriate for those with multiple risk factors. ▶ Chap. 55, "Athletic Injuries," discusses VTE prophylaxis for hospitalized and surgical patients in more detail.

Superficial Vein Thrombosis and Superficial Thrombophlebitis

Traditionally considered to be a more benign and self-limiting condition, thrombosis of the superficial venous system is often considered distinct from deep vein thrombosis and, as a result, studied less [46]. Superficial vein thrombosis (SVT) is currently the preferred term for a thrombus in the superficial vein system (especially the axial veins like the great and small saphenous veins), while the term superficial thrombophlebitis can more appropriately be used to describe confirmed

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thrombus accompanying phlebitis (inflammation within a vein) of the tributary veins. Phlebitis can develop for a variety of reasons including injury, infection, or thrombus [47]. The distinction between SVT and superficial thrombophlebitis is important because thrombosis of axial veins can lead to thromboembolism, especially if the proximal aspect of the larger axial veins is affected [46]. Patients with superficial venous thrombosis are at higher risk of developing DVT [31].

The risks for developing SVT and superficial thrombophlebitis are similar to those previously described for VTE (Table 1) and include advanced age, obesity, active cancer, previous thromboembolic episodes, pregnancy, oral contraceptive use, hormone replacement therapy, recent surgery, autoimmune diseases, and varicose veins (this last one being unique to SVT) [46]. Phlebitis and thrombosis of the lower extremities are more likely to occur in varicose veins, which account for over 60% of SVT cases, while lack of physical activity and trauma are among the risk factors for the development of a clot in varicosities [48]. The most consistent risk factor for developing phlebitis or thrombosis of the upper extremities involves the use of venous cannulation, and while this discussion focuses more on lower extremity conditions, the same principles may be applied to the upper extremities with regard to SVT [49]. Saphenous vein thrombosis is thought to be more common than DVT, and the great saphenous vein is more commonly involved than the small saphenous vein [48, 49].

On exam, one can expect to find pain, redness, and swelling along the path of a superficial vein [48]. If a thrombus is present, it may appear as a thickened cord, especially if it persists when the extremity is raised, and may be accompanied by low-grade fever. High fever or redness extending significantly past the margin of the vein should prompt evaluation for suppurative infection, and is usually associated with invasive procedures [46]. Superficial thrombus is usually identified with the use of duplex ultrasound, which will also help to identify whether DVT is present; however, some favor a period of observation in isolated findings of thrombophlebitis remote from the great and small saphenous veins [46].

Patients with isolated uncomplicated phlebitis not involving the saphenous veins, with no other risk factors for DVT, can be treated symptomatically with repeat evaluation in 7–10 days. Treatment depends on several variables, including size, location, and severity of symptoms [46]. For the management of uncomplicated thrombi at low risk for VTE (>5 cm from the saphenofemoral or saphenopopliteal junction, <5 cm in length, and no other risk factors), supportive therapy with elevation of the affected extremity, cool/warm compresses, non-steroidal anti-inflammatory drugs (NSAIDS), encouraging patient mobility, and possibly compression stockings in appropriate candidates are preferred initial therapies [46]. Most uncomplicated cases respond to supportive care within a few days and pain usually resolves in a week. Ultrasound should be performed if extension does occur, and the thrombosed vessel may still be palpable for months after resolution of pain [46, 50].

For higher-risk thrombi (i.e., SVT ≤5 cm from the saphenofemoral or saphenopopliteal junction, a thrombosed segment ≥5 cm in length, or other medical risk factors for VTE), anticoagulation should be considered [46]. Suggested therapies include subcutaneous fondaparinux (2.5 mg daily), subcutaneous low-molecular-weight heparin (enoxaparin 40 mg daily), or oral rivaroxaban (10 mg daily) for 45 days [46, 50]. If anticoagulation is not possible, or if thrombus recurs, ligation or excision may be needed to prevent extension. Antibiotics should be used only if signs of infection are present [46].

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Selected Disorders of the Cardiovascular System

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Peripheral Artery Disease

The prevalence of peripheral artery disease (PAD) increases with age from <5% before age 60 to over 20% after age 74 with over 80% of PAD patients identified as current or former smokers [1]. Coronary artery disease (CAD) and cerebrovascular disease occur two to four times more often in patients with lower extremity PAD compared to those without PAD. The amputation rate in the general PAD population is 1% or less per year but is significantly more common in current smokers and diabetics (7–15-fold increase). Recent trials have reported a combined rate of myocardial infarction (MI), stroke, and vascular death of 4–6%, while epidemiological studies report annual mortality of 4–6%. Unfortunately, too few patients with PAD receive guideline-directed management and therapy (GDMT) to reduce morbidity and mortality from CAD and other cardiovascular diseases [2].

Presentation and Diagnosis

Intermittent claudication, defined as fatigue, discomfort, cramping, or pain that occurs in lower extremity muscle groups during exercise which is relieved by rest (in 10 min or less), is the presenting symptom in 10–35% of patients. Atypical lower extremity pain (including numbness, tingling, or paresthesia) is the presenting symptom in 40–50% of cases, although in many of these patients, PAD is an incidental finding and not the cause of their leg pain. When combined with cases found through screening, 20–50% of patients are asymptomatic from their PAD at the time of diagnosis. Acute limb ischemia (ALI), where symptoms are present for less than 2 weeks, is characterized by the 6 "Ps": pain, paralysis, paresthesias, pulselessness, pallor, and poikilothermia. ALI represents a medical emergency which is subdivided into three severities: viable (no immediate threat), threatened, and irreversible (major tissue loss or permanent nerve damage is inevitable). Critical limb ischemia (CLI) includes chronic rest pain (≥2 weeks), nonhealing ulcers/wounds, or gangrene due to occlusive arterial disease. CLI is the presentation in 1–2% of cases, and after 1 year only 50% will be alive with both legs (25% will die and 25% will have at least one amputation). Additional signs on physical exam include diminished pulses and vascular bruits, while dependent rubor, early pallor when elevating the limb, reduced capillary refill, hair loss, and muscle wasting are signs of chronic ischemia. Arterial ulcerations are typically quite painful unless neuropathy is also present as can occur in patients with concomitant diabetes mellitus.

A resting ankle-brachial index (ABI) in both legs is recommended for diagnosis of lower extremity PAD and should be reported as follows: noncompressible >1.40, normal 1.00 to 1.40, borderline 0.91 to 0.99, or abnormal ≤0.90 [2]. A toe-brachial index should be used in patients with noncompressible vessels (≤0.70 diagnoses PAD). Patients with typical exertional claudication and a normal or borderline resting ABI should complete an exercise treadmill ABI. Further imaging is reserved for patients in whom revascularization is considered or who continue to experience lifestyle-limiting claudication despite GDMT. Anatomic assessment may be completed with duplex ultrasound (which localizes diseased segments and grades lesion severity), MR angiography (especially good for evaluation of arterial dissection and wall morphology), or CT angiography (when MR is contraindicated). Invasive angiography is often the first-line choice for patients with CLI but remains a second-line

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choice for patients without CLI if they are candidates for revascularization.

Differential Diagnosis

Atherosclerosis is the most common cause of PAD, just as it is for CAD and stroke. Lower extremity PAD may also be caused by thromboembolism, trauma, vasculitis, physiological entrapment syndromes, fibromuscular dysplasia, or congenital abnormalities [2]. The differential considerations for claudication include neurogenic claudication (due to lumbar disk disease, spinal stenosis, or osteophytic changes), osteoarthritis (hip, foot, or ankle), severe venous obstructive disease, chronic compartment syndrome, symptomatic Baker's cyst, or shin splints (in younger persons). The differential considerations for nonhealing wounds include trauma, infection, malignancy, autoimmune injury, drug reactions, neuropathic, microangiopathy, or venous ulceration.

Intervention

Atherosclerotic cardiovascular disease (ASCVD) risk factors, including hypertension and diabetes, should be managed according to current evidence-based guidelines [2]. Statins are recommended for all patients with PAD. Tobacco cessation is essential, and pharmacologic therapies should be combined with behavioral treatment if there are no contraindications. Antiplatelet therapy (aspirin 75–325 mg or clopidogrel 75 mg daily) is recommended for all patients with PAD to decrease the risk of myocardial infarction, ischemic stroke, and vascular death. Vorapaxar (2.5 mg daily with aspirin or clopidogrel), a novel antiplatelet agent which is contraindicated in patients with a history of transient-ischemic attack or stroke, and rivaroxaban (2.5 mg BID with low dose aspirin) are also FDA approved for patients with both PAD and CAD; however, their use is limited by an increased risk of bleeding complications [3]. Supervised exercise training for a minimum of 30–45 minutes, three times per week for at least 12 weeks, improves intermittent claudication [2]. Cilostazol (100 mg twice per day) is the first-line pharmacologic treatment for claudication in the absence of heart failure (HF). Pentoxifylline is no longer recommended as a second-line therapy since the evidence now shows that it has no benefit. Oral vasodilator prostaglandins, vitamin E, chelation therapy, and homocysteine lowering with B-complex vitamins should also not be used to treat PAD. While warfarin anticoagulation should not be used to decrease the risk of cardiovascular ischemic events, it may have a role in improving graft patency. Consultation for surgical or endovascular revascularization is indicated for occupation or lifestyle-limiting symptoms where nonsurgical therapy has failed or for signs or symptoms of ischemia at rest.

Pericarditis

Acute pericarditis is an inflammation of the pericardium, the avascular fibrous sac that surrounds the heart. Constrictive pericarditis is a term reserved for post-inflammatory changes affecting the pericardium, resulting in impaired diastolic filling of the heart. Acute pericarditis is relatively common and accounts for 5% of emergency room admissions for chest pain [4]. Some cases are mild and patients may not present for medical care; others can be life-threatening. There are numerous etiologies of pericardial inflammation (Table 1). In developed countries, 80–90% of cases are idiopathic, as no specific cause is found after routine evaluation. These cases are typically thought to be viral in origin. The remaining cases are most often found to be related to post-cardiac injury syndromes, autoimmune disease, and malignancy. Tuberculosis remains the leading cause of pericardial disease in the developing world.

Presentation and Diagnosis

Patients typically present with chest pain. The pain is often sharp, severe, retrosternal, exacerbated with breathing, and relieved with sitting

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Table 1 Etiologies of pericarditis

Infectious
Viral: Coxsackievirus, echovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, parvovirus B19, human herpesvirus 6
Bacterial: Tuberculosis, *Coxiella burnetii*, rare other bacteria (pneumococcus, meningococcus, gonococcus, haemophilus, streptococcus, staphylococcus, chlamydia, mycoplasma, legionella, leptospira, listeria)
Fungal: Histoplasma (more likely in immunocompetent patients), aspergillus, *Blastomyces*, candida (more likely in immunosuppressed patients)
Parasitic: *Echinococcus*, toxoplasma (overall very rare)
Autoimmune
Pericardial injury syndromes: Post-myocardial infarction syndrome, post-pericardiotomy syndrome
Connective tissue diseases: Systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, systemic sclerosis, systemic vasculitides, Behçet's syndrome, sarcoidosis, amyloidosis
Autoimmune diseases: Familial Mediterranean fever, tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
Neoplastic
Primary tumors: Pericardial mesothelioma (overall rare)
Secondary metastatic tumors: Lung cancer, breast cancer, lymphoma
Other
Trauma: Blunt chest trauma, penetrating thoracic injury, esophageal perforation, radiation
Metabolic: Uremia, myxedema (rare)
Drugs: Lupus-like syndrome (procainamide, hydralazine, isoniazid, phenytoin), hypersensitivity pericarditis with eosinophilia (penicillins), direct toxic effects (doxorubicin and daunorubicin; often associated with cardiomyopathy)

Source: Little and Freeman [5]

forward. This pain may mimic other diagnoses. Acute pericarditis is diagnosed if at least two of four key findings are present: chest pain consistent with pericarditis, pericardial friction rub ("Velcro-like" sounds heard best at the apex), typical electrocardiogram (ECG) changes (diffuse upsloping ST elevation with PR depression), or significant pericardial effusion (seen on echocardiogram) [4]. The auscultative and electrographic signs may be transient, and repeated examination may be warranted.

Patients with pericarditis may report a viral prodrome. Many have sinus tachycardia and low-grade fever. Signs of systemic inflammation commonly arise, such as elevated white blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Troponin may be elevated. Rarely, patients will present with cardiac tamponade and likely will have chest pain and dyspnea. Exam shows jugular venous distention, muffled heart sounds, hypotension, and a paradoxical pulse.

Once the diagnosis of pericarditis is confirmed, the next step is to search for the cause of inflammation. This can be tailored to the patient's presentation and history, to identify possible treatable or life-threatening etiologies outlined in Table 1. Diagnostic pericardiocentesis is typically done only for large effusions. If the diagnosis is not confirmed, but clinical suspicion remains for pericarditis, routine lab evaluation can be done with frequent reexamination and repeat ECG. At times, CT or MRI is used to show pericardial thickening.

Differential Diagnosis

Differential considerations for acute pericarditis include most cardiac syndromes. This includes acute myocardial infarction (AMI), pulmonary embolus, aortic dissection, cardiac contusion, and myocarditis. Consideration must also be given to the other structures in the thorax, to include mediastinitis, esophageal spasm, esophagitis, gastroesophageal reflux, costochondritis, and pneumonia. The ECG changes of pericarditis may be confused with early repolarization [4]. Often the most difficult distinction to make is between acute pericarditis and AMI. Cardiac catheterization may

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be performed. There will be a lack of angiographic evidence of CAD in cases of acute pericarditis.

Intervention

Initial management of acute pericarditis focuses on treating the underlying cause, if possible. Otherwise, most idiopathic or viral pericarditis resolves spontaneously or with simple, first-line treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are the basis of the treatment regimen. Often aspirin is used, especially in post-MI patients, but at higher anti-inflammatory doses (650 mg every 6 h) [5]. Indomethacin (50 mg every 8 h) and ibuprofen (600 mg every 8 h) can also be used. NSAIDs can be discontinued or tapered after 7–10 days if the patient's pain is resolved. Some clinicians use the CRP level to guide discontinuation. A proton-pump inhibitor is often used in conjunction for gastric protection. Colchicine (0.5 mg twice daily if weight >70 kg, once daily if weight <70 kg) is used in addition to NSAIDs to decrease the likelihood of persistent symptoms and the risk of recurrent pericarditis [4]. Colchicine is typically continued for 3 months. Corticosteroids do have strong anti-inflammatory properties, but their use is associated with an increased chance of recurrence. They may be required in refractory cases. Patient's lacking high-risk indicators can be managed in the outpatient setting (Table 2). Bacterial pericarditis, while rare, can be life-threatening. In addition to antibiotics, intrapericardial fibrinolysis can be effective to prevent evolution to constrictive pericarditis.

Adequate treatment of acute pericarditis is key to prevent recurrent pericarditis or constrictive pericarditis. If symptoms recur, NSAID therapy should be reinstated. Colchicine should be added if it was not used in the initial case. The most significant complication of acute pericarditis is constrictive pericarditis. Since diastolic filling of the heart is impaired by a fibrotic pericardium, patients develop symptoms of HF and fluid overload. If the initial case of acute pericarditis was not recognized, the diagnosis may not be initially clear. At times the constriction is transient, but patients often require pericardiectomy for treatment.

Table 2 Predictors of poor outcome in pericarditis

Fever >38 °C
Symptoms developing over several weeks in association with an immunosuppressed state
Traumatic pericarditis
Pericarditis in a patient receiving oral anticoagulants
Large pericardial effusion (>20 mm echo-free space or evidence of tamponade)
Failure to respond to nonsteroidal anti-inflammatory drugs

Source: Little and Freeman [5]

Bacterial Endocarditis

Infectious endocarditis (IE) is an infection of the endocardial surface mainly due to bacteria but rarely may be caused by fungi and protozoa [6]. Bacterial endocarditis (BE) may give rise to the classic though not universally found lesion of IE: the valvular vegetation. These vegetations may interfere with valvular function leading to HF and may embolize to produce a wide variety of focal and systemic signs and symptoms. The overall incidence of IE in the United States has risen to 13 cases per 100,000 patient-years, with a slight male predominance (58%) and a median age of 61 years [7, 8]. While valvular disease is still a major risk factor, it is now uncommonly due to rheumatic heart disease, having dropped from 50% of cases to less than 5% over the last 40 years. Untreated BE is almost uniformly fatal; therefore, if BE is suspected, aggressive evaluation and treatment, to include early surgery in some cases, are essential. In-hospital mortality rates have been stable over the past 25 years at 15–20% with 1-year mortality of almost 40%.

Effective management of BE relies on targeting treatment to specific organisms. Gram-positive bacteria (predominantly *streptococci*, *staphylococci*, and *enterococci*) are the most common cause of IE and now account for over 90% of the cases with a known organism, in part due to an increasing incidence of *Staphylococcus aureus* [7]. Fungal, protozoal, and gram-

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negative causes increase with prosthetic valve endocarditis (PVE) and other invasive cardiovascular devices [6]. The HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) occurs in 2% of cases worldwide. Intravenous drug users (IVDUs) have a very high incidence of right-sided valvular involvement, especially the tricuspid valve which is uncommon in non-IVDUs. Nosocomial BE is most commonly related to indwelling catheters or invasive procedures. BE caused by HACEK most commonly occurs in native valve, non-IVDUs.

Presentation and Diagnosis

Though the primary lesion in BE is in the heart itself, many of its presenting signs and symptoms reflect the systemic nature of the disease [6]. Fever, myalgias, fatigue, headache, and abdominal pain are common in all types of BE. Heart failure is the most common complication and develops in approximately 30% of cases. Vegetations can embolize to almost any location, causing distant infection or infarction. Right-sided embolic events may lead to specific complaints of chest pain, cough, and hemoptysis. Left-sided embolic events can present as mental status changes, stroke, myocardial infarction, splenic infarction, and renal abscess. Stroke occurs in approximately 9–13% of patients, while myocardial infarction occurs in 3–7% of cases [7]. Other complications of BE include osteomyelitis, septic arthritis, and mycotic aneurysms.

With the exception of Janeway lesions, which occur in only 5% of cases, few physical findings are highly specific for BE. Likewise, Roth's spots (2%), Osler's nodes (3%), splinter hemorrhages (8%), and splenomegaly (11%) are relatively uncommon since the diagnosis of IE is now occurring earlier in the clinical course [7, 8]. Cardiac murmurs are most often regurgitant with a new murmur occurring 48% of the time and worsening of an old murmur is present in an additional 20% of cases. With the exception of blood cultures, laboratory evaluation is frequently of less value in making the early diagnosis of BE compared to the history and examination. Antibiotic therapy should not be given prior to blood culture collection, particularly in patients with known valvular heart disease and an unexplained fever [8, 9]. Antimicrobial therapy can be delayed in patients with a chronic or subacute presentation to allow for the collection of three sets of blood cultures from peripheral sites with the first and third drawn at least 1 h apart from each other [6]. At least two, but preferably three, sets of blood cultures separated by 30 min should be obtained from patients who present in severe sepsis or septic shock. Other laboratory findings and imaging may reflect other complications as mentioned above. Blood culture negative IE (as high as 31% of IE) may require serologic testing or PCR of surgical specimens to identify the causative organism [9]. ECG may reveal conduction abnormalities, indicating the extension of an aortic valve infection to a valve ring abscess, which carries a worse prognosis.

The 1994 Duke criteria were modified in 2000 to redefine "possible IE" (reducing the number of patients in this category) and modify the major and minor criteria (increasing the sensitivity) [10]. The diagnosis of "definite IE" is arrived at either through one of two pathologic criteria or through one of several combinations of major and minor clinical criteria (Table 3). The clinical criteria emphasize two main areas: positive blood cultures and evidence of endocardial involvement (Table 4). The second major criterion takes advantage of both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) as a safe yet highly sensitive means for identifying endocardial lesions. Guidance as to when TEE is preferred over TTE was added to the major criteria definitions as part of the modifications in 2000.

The Duke criteria have been extensively studied and found to have a sensitivity around 80% while maintaining a specificity of 92–99% [6, 8, 9]. These criteria have also been validated for both the adult and pediatric populations, as well as special groups such as those with PVE. However, since an adequate amount of clinical data must be collected before the Duke criteria can be applied, early empiric therapy should not

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Table 3 Definition of infective endocarditis according to the modified Duke criteria, with modifications shown in boldface

Definite infective endocarditis
Pathologic criteria
Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen
Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria[a]
2 major criteria
1 major criterion and 3 minor criteria
5 minor criteria
Possible infective endocarditis
1 major criterion and 1 minor criterion
3 minor criteria
Rejected
Firm alternate diagnosis explaining evidence of infective endocarditis
Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days
No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days
Does not meet criteria for possible infective endocarditis, as above

Source: Li et al. [10], "Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis," *Clinical Infectious Diseases*, 2000; 30:633–8, by permission of the Infectious Diseases Society of America
[a]See Table 4 for definitions of major and minor criteria

be delayed if IE is suspected. In this regard, the criteria are best used to assist in sculpting medical therapy and determining a need for surgical intervention.

Differential Diagnosis

Virtually any systemic infection should be considered in the differential diagnosis of IE. These include, but are not limited to, pneumonia, meningitis, pericarditis, abscess, osteomyelitis, tuberculosis, and pyelonephritis. Noninfectious etiologies to be considered include stroke, myocardial infarction, rheumatic fever, vasculitis, malignancy, and fever of unknown origin.

Intervention

Once the diagnosis of IE is suspected, antibiotic therapy should be instituted without delay after blood cultures are obtained [6, 9]. Because bacteria in valvular vegetations are relatively protected from host immune defenses, antibiotics chosen to treat IE must be bactericidal, and regimens for their administration must be aggressive and of adequate duration to completely eradicate the organism and prevent relapse. Empiric therapy should be guided by local resistance patterns, but as a general rule for all native valves and prosthetic valves greater than 12 months after surgery, treatment may begin with ampicillin-sulbactam (3.0 g IV q6h) and gentamicin (1.5 mg/kg IV/IM q12h or 1.0 mg/kg IV/IM q8h). In patients with a β-lactam allergy, vancomycin (15/mg IV q12h) and ciprofloxacin (400 mg IV q12h or 500 mg PO q12h) may replace ampicillin-sulbactam. Empiric therapy for prosthetic valves less than 12 months after surgery may begin with vancomycin (15 mg/kg IV q12h), gentamicin (1.5 mg/kg IV/IM q12h or 1.0 mg/kg IV/IM q8h), and rifampin (600 mg PO q12h). The full course of antibiotics is tailored to culture results with some native valve regimens as short as 2 weeks, while all PVE regimens last a minimum of 6 weeks (Tables 5 and 6).

At least two sets of blood cultures should be collected every 24–48 h until a negative culture is

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Table 4 Definition of terms used in the modified Duke criteria for the diagnosis of infective endocarditis (IE) with modifications shown in boldface

Major criteria
Positive blood culture for IE
Typical microorganisms consistent with IE from 2 separate blood cultures:
Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*
Community-acquired enterococci, in the absence of a primary focus
Microorganism consistent with IE from persistently positive blood cultures, defined as follows:
At least 2 positive cultures of blood samples drawn >12 h apart
All of 3 or a majority of ≥4 separate cultures of blood (with first and last drawn at least 1 h apart)
Single positive blood culture for *Coxiella burnetii* or antiphase I IgG titer ≥1:800
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation
Abscess
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or change in preexisting murmur not sufficient)
Minor criteria
Predisposition: Predisposing heart condition or injection drug use
Fever: Temperature >38 °C
Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhages, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiologic evidence: Positive blood culture but does not meet a major criterion as noted above[a] *or* serological evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

Note: *TEE* transesophageal echocardiography, *TTE* transthoracic echocardiography
Source: Li et al. [10], "Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis," *Clinical Infectious Diseases*, 2000; 30:633–8, by permission of the Infectious Diseases Society of America
[a]Excludes single-positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis

obtained. The first day of therapy for determining the duration of antibiotics is the day when blood cultures were initially negative (if initial cultures were positive). If a native valve is replaced or repaired with prosthetic material during the initial course of antibiotics, European guidelines recommend continuation of native valve treatment, while US guidelines now state that there is no consensus regarding regimen selection in this situation. If the resected tissue is culture positive, then the first day of a complete course for PVE should be the day of surgery (if blood cultures were negative before the operation). If the resected tissue is culture negative, the previously completed days of treatment can be subtracted from the total required duration of treatment. When multiple antibiotics are recommended, they should be given simultaneously or in short succession to maximize pharmacologic synergy.

Careful attention should be given to identifying and treating complications. HF in particular must be treated aggressively, since there is a dramatic worsening of prognosis as HF becomes more severe. Therapy of HF should be initiated with GDMT, but the timing of surgical intervention should be given particular emphasis as the mortality without surgery when HF is present may exceed 50%. To that end, early consultation with cardiovascular surgery, infectious disease, and cardiology is warranted for all patients with

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Table 5 Antibiotic regimens for native valve endocarditis

Viridans group streptococci and *Streptococcus gallolyticus (bovis)* (highly penicillin susceptible: MIC ≤0.12 μg/mL)
Penicillin G IV or ceftriaxone IV/IM for 4 weeks[a]
[Penicillin G IV or ceftriaxone IV/IM] and gentamicin IV/IM for first 2 weeks[a,b]
Vancomycin IV for 4 weeks (with trough of 10–15 μg/mL)
Viridans group streptococci and *Streptococcus gallolyticus (bovis)* (relatively penicillin resistant: MIC >0.12 to ≤0.5 μg/mL)
Penicillin G IV for 4 weeks and gentamicin IV/IM for first 2 weeks[a]
Ceftriaxone IV/IM for 4 weeks if the isolate is susceptible
Vancomycin IV for 4 weeks (with trough of 10–15 μg/mL)
Viridans group streptococci (fully penicillin resistant: MIC >0.5 μg/mL), *Abiotrophia defectiva*, and *Granulicatella* species
Infectious disease consultation required to determine duration:
[Ampicillin IV or penicillin G IV] and gentamicin as done for *Enterococcus* species
Ceftriaxone IV/IM if the isolate is susceptible and gentamicin
Vancomycin IV (with trough of 10–15 μg/mL)
Streptococcus pneumoniae, *Streptococcus pyogenes*, groups B, C, F, and G β-hemolytic streptococci
Consult infectious disease as there is little published evidence to guide therapy
Staphylococci
Oxacillin-susceptible
Nafcillin IV (preferred if brain abscess also present) or oxacillin IV for 6 weeks
For 2 weeks for uncomplicated right-sided IE
Cefazolin IV for 6 weeks (in patients with non-anaphylactic penicillin reactions)
Vancomycin IV for 6 weeks (with trough of 10–20 μg/mL, in patients with immediate-type hypersensitive reactions to β-lactams)
Daptomycin IV for 6 weeks (in patients with immediate-type hypersensitive reactions to β-lactams; or for 2 weeks for uncomplicated right-sided IE)
Oxacillin-resistant
Vancomycin IV for 6 weeks (with trough of 10–20 μg/mL)
Daptomycin IV for 6 weeks (or for 2 weeks for uncomplicated right-sided IE)
Enterococcus susceptible to penicillin, vancomycin, and gentamicin or streptomycin
Gentamicin should be given in three divided doses, with peak of 3–4 μg/mL and trough of <1 μg/mL
[Ampicillin IV or penicillin G IV] and gentamicin IV/IM for 4 weeks (symptom duration <3 months)
[Ampicillin IV or penicillin G IV] and gentamicin IV/IM for 6 weeks (symptom duration ≥3 months)
Vancomycin IV (if unable to tolerate β-lactam; with trough of 10–20 μg/mL) and gentamicin IV/IM for 6 weeks
Ampicillin IV and ceftriaxone IV for 6 weeks (for patients with CrCl <50 mL/min, or if gentamicin resistant and rapid streptomycin serum concentrations not available)
Streptomycin may replace gentamicin, if isolate is sensitive to the former and resistant to the latter, with a peak of 20–35 μg/mL and a trough of <10 μg/mL
Enterococcus resistant to penicillin but susceptible to aminoglycoside and vancomycin
Gentamicin should be given in three divided doses, with peak of 3–4 μg/mL and trough of <1 μg/mL
β-lactamase-producing strain
Ampicillin-sulbactam IV and gentamicin IV/IM for 6 weeks
Vancomycin IV and gentamicin IV/IM for 6 weeks
Intrinsic penicillin resistance
Vancomycin IV and gentamicin IV/IM for 6 weeks
Enterococcus resistant to penicillin, aminoglycoside, and vancomycin
Linezolid IV/PO for >6 weeks
Daptomycin IV for >6 weeks
HACEK microorganisms
Ceftriaxone IV/IM for 4 weeks (cefotaxime or another 3rd-/4th-generation cephalosporin may be used)

(continued)

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Table 5 (continued)

Ampicillin-sulbactam IV for 4 weeks
Ciprofloxacin IV/PO for 4 weeks (third-line treatment due to limited published in vivo evidence for IE; levofloxacin or moxifloxacin may be used)
Culture-negative endocarditis
Cefepime IV and vancomycin IV for acute presentations (days of symptoms)
Ampicillin-sulbactam IV and vancomycin IV for subacute presentations (weeks of symptoms)
Duration to be determined with infectious disease consultant

Source: Baddour et al. [6]
[a]Ampicillin is a reasonable alternative to penicillin if a penicillin shortage exists
[b]The 2-week regimen is not appropriate for patients with known abscesses, impaired 8th cranial nerve function, creatinine clearance <20 mL/min, or infection with *Abiotrophia*, *Granulicatella*, or *Gemella* species

suspected IE. Nearly 50% of patients will undergo surgical intervention, and in general, surgery should not be delayed because of active IE [6, 8]. Reinfection of newly implanted valves occurs in 2–3% of cases; however, surgery is associated with a marked reduction of in-hospital mortality. Indications for surgical intervention are listed in Table 7.

Patients who survive an episode of IE remain at increased risk for recurrent infection for the rest of their life. All patients should undergo a complete dental evaluation for the eradication of sources and education on the need for lifelong follow-up care with a dental professional. IVDUs should be referred to a drug treatment program. At the completion of therapy, all patients should have an echocardiogram repeated in order to establish a new baseline for valvular function and morphology. They should be educated on the signs and symptoms of IE and HF as well as any procedural antibiotic prophylaxis that may be needed in the future. Patients who were exposed to aminoglycosides are at risk for ototoxicity, and *Clostridium difficile* diarrhea may present up to 4 weeks after the last dose of antibiotics. All survivors of IE should have ≥3 sets of blood cultures drawn prior to starting antibiotics for a subsequent febrile illness.

Prevention

Prevention of IE in those with abnormal valvular architecture is covered in detail in ▶ Chap. 60, "Medical Care of the Surgical Patient." In those with normal native valves, prevention is mainly an issue of education on the avoidance of IV drug use.

Cardiomyopathy

The American Heart Association (AHA) published a scientific statement in 2006 which updated the definition and classification of the cardiomyopathies (CMs) [11]. The primary CMs mainly, or only, involve the heart muscle, while the myocardial dysfunction of the secondary CMs represents just one of the many organs damaged by a systemic disorder. This chapter focuses on the primary CMs which are further subdivided into three categories: genetic, mixed (genetic and nongenetic), and acquired. The AHA definition of the CMs specifically excludes myocardial dysfunction directly caused by other cardiovascular abnormalities such as systemic hypertension, valvular heart disease, congenital heart disease, and ischemia from ASCVD.

Most CMs present with the typical manifestations of either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) [12]. Management of the CMs typically includes early consultation with a cardiologist well versed in the pertinent and complex issues surrounding diagnosis and treatment. Possible treatments include lifestyle changes, pharmacologic modification of the neurohormonal axes which contribute to HF progression (angiotensin-converting enzyme inhibitors [ACE-Is], angiotensin receptor blockers [ARBs], aldosterone

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Table 6 Antibiotic regimens for endocarditis of prosthetic valve or valvular prosthetic material

Viridans group streptococci and *S. gallolyticus (bovis)* (penicillin susceptible: MIC ≤0.12 μg/mL)
[Penicillin G IV or ceftriaxone IV/IM] for 6 weeks ± gentamicin IV/IM for 2 weeks[a]
Vancomycin IV for 6 weeks (with trough of 10–15 μg/mL)
Viridans group streptococci and *S. gallolyticus (bovis)* (penicillin resistant: MIC >0.12 μg/mL)
[Penicillin G IV or ceftriaxone IV/IM] for 6 weeks and gentamicin IV/IM for 6 weeks[a]
Vancomycin IV for 6 weeks (with trough of 10–15 μg/mL)
Streptococcus pneumoniae, *Streptococcus pyogenes*, groups B, C, F, and G β-hemolytic streptococci
Consult infectious disease as there is little published evidence to guide therapy
Staphylococci
Oxacillin-susceptible
[Nafcillin IV or oxacillin IV] plus rifampin IV/PO for ≥6 weeks and gentamicin IV/IM for first 2 weeks
Cefazolin IV replaces nafcillin/oxacillin in patients with non-anaphylactic penicillin reactions
Oxacillin-resistant (or in patients with immediate-type hypersensitive reactions to β-lactams)
Vancomycin IV for ≥6 weeks plus rifampin IV/PO for ≥6 weeks and gentamicin IV/IM for first 2 weeks
Enterococcus susceptible to penicillin, vancomycin, and gentamicin or streptomycin
Gentamicin should be given in three divided doses, with peak of 3–4 μg/mL and trough of <1 μg/mL
[Ampicillin IV or penicillin G IV] and gentamicin IV/IM for 6 weeks (symptom duration ≥3 months)
Vancomycin IV (if unable to tolerate β-lactam; with trough of 10–20 μg/mL) and gentamicin IV/IM for ≥6 weeks
Ampicillin IV and ceftriaxone IV for 6 weeks (for patients with CrCl <50 mL/min, or if gentamicin resistant and rapid streptomycin serum concentrations not available)
Streptomycin may replace gentamicin, if isolate is sensitive to the former and resistant to the latter, with a peak of 20–35 μg/mL and a trough of <10 μg/mL
Enterococcus resistant to penicillin but susceptible to aminoglycoside and vancomycin
Gentamicin should be given in three divided doses, with peak of 3–4 μg/mL and trough of <1 μg/mL
β-lactamase-producing strain
Ampicillin-sulbactam IV and gentamicin IV/IM for 6 weeks
Vancomycin IV and gentamicin IV/IM for 6 weeks
Intrinsic penicillin resistance
Vancomycin IV and gentamicin IV/IM for 6 weeks
Enterococcus resistant to penicillin, aminoglycoside, and vancomycin
Linezolid IV/PO for >6 weeks
Daptomycin IV for >6 weeks
HACEK Microorganisms
Ceftriaxone IV/IM for 6 weeks (cefotaxime or another 3rd-/4th-generation cephalosporin may be used)
Ampicillin-sulbactam IV for 6 weeks
Ciprofloxacin IV/PO for 6 weeks (third-line treatment due to limited published in vivo evidence for IE; levofloxacin or moxifloxacin may be used)
Culture-negative endocarditis
Early (≤1 year after surgery)
Vancomycin, cefepime, rifampin, and gentamicin
Late (>1 year after surgery)
Vancomycin and ceftriaxone
Duration to be determined with infectious disease consultant

Source: Baddour et al. [6]

[a]Ampicillin is a reasonable alternative to penicillin if a penicillin shortage exists

antagonists, beta-blockers, ARB-neprilysin inhibitor), invasive electrophysiology (cardiac resynchronization, implanted cardioverter defibrillator [ICD]), arrhythmia suppression (pharmacologic and nonpharmacologic), surgery (septal myomectomy, heart transplantation), and therapies targeted

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Table 7 Indications for surgery in infectious endocarditis (IE)

Early surgery (before completion of antibiotics, during initial hospitalization)[a]
Valve dysfunction causing signs or symptoms of heart failure
Left-sided IE caused by *S. aureus*, fungi, or other highly resistant organisms
New heart block
Annular or aortic abscess
Destructive (valve dehiscence, rupture) or penetrating lesions/fistulas
Persistent bacteremia or fevers for more than 5–7 days after starting appropriate antibiotics
Recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy
Native valve endocarditis with severe regurgitation and mobile vegetations >10 mm
Relapse of prosthetic valve endocarditis
Complete removal of pacemaker or defibrillator with proven infection of pocket or leads
Surgery (variable timing)
Repair rather than replacement of right-sided IE when possible, especially in intravenous drug users
Prosthetic valve endocarditis with recurrence of bacteremia after complete course of antibiotics and negative blood cultures with no other source of infection
Complete removal of pacemaker or defibrillator when valvular IE is caused by S. aureus or fungi
Complete removal of pacemaker or defibrillator when undergoing valve surgery for IE

Source: Baddour et al. [6] and Nishimura, et al. [8]

[a]Early surgery is still appropriate in patients with a stroke provided there is no evidence or extensive neurological damage and no intracranial hemorrhage. If either of those findings is present, surgery should be delayed at least 4 weeks in a hemodynamically stable patient

at specific underlying causes (chelation, phlebotomy, bone marrow transplant, etc.).

Hypertrophic Cardiomyopathy (Genetic)

Hypertrophic cardiomyopathy (HCM) is defined as "a disease state characterized by unexplained left ventricular (LV) hypertrophy associated with non-dilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient" [13]. Over 1500 autosomal dominant mutations have been identified in at least 8 genes that encode sarcomere proteins (3 other genes are still considered potentially causative). HCM is seen throughout the world with a global prevalence of approximately 0.2% which in the United States represents at least 600,000 individuals.

Presentation and Diagnosis

Most affected individuals likely have a normal life expectancy; however, in those who develop symptoms, HCM manifests in three different patterns which are not mutually exclusive: sudden cardiac death (SCD), atrial fibrillation/stroke, and HF that may progress to end-stage disease. SCD due to ventricular tachyarrhythmia may be the initial presentation of HCM with the highest risk in patients <35 years of age.

Dynamic left ventricular outflow tract (LVOT) obstruction, defined as an outflow gradient ≥30 mmHg, is typically caused by a narrowing between the hypertrophied ventricular septum and anterior displacement of the mitral valve during systole. Basal obstruction is present at rest, while labile obstruction is only present when physiologically provoked. LVOT obstruction is increased by activities that increase myocardial contractility (e.g., strenuous exercise) or by maneuvers or agents that decrease afterload (e.g., Valsalva, diuretics). Conversely, obstruction is decreased by agents that decrease myocardial contractility (e.g., beta-blockers) or by maneuvers that increase afterload (e.g., squatting).

In addition to common HF symptoms such as fatigue, dyspnea, and orthopnea, patients with

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HCM often complain of palpitations (due to atrial fibrillation caused by left atrial enlargement), pre-syncope, and syncope. Since most HCM is nonobstructive (outflow gradient <30 mmHg at rest and with provocation), auscultation generally reveals no murmur. Patients with LVOT often demonstrate a 3–4/6 systolic murmur heard over both the left sternal border (due to outflow obstruction) and apex with radiation to the axilla (due to mitral regurgitation). An S_4 is often heard due to increased filling from the enlarged atria. Pulmonary congestion is rare except with severe outflow obstruction or end-stage HCM (when systolic and diastolic dysfunction become manifest) or with atrial fibrillation. The ECG usually reveals a wide array of nonspecific changes including LV hypertrophy, ST changes, T wave inversion, left atrial enlargement, and Q waves. 24-hour electrocardiographic monitoring is recommended to identify patients who may be a candidate for an ICD, due to ventricular tachycardia, and may also identify atrial fibrillation or flutter. The chest radiograph is often normal or suggestive of atrial enlargement. TTE with Doppler imaging is essential and may be combined with exercise testing to identify labile obstruction. The transesophageal approach may help define subtle mitral valve abnormalities or guide surgical intervention. Cardiovascular magnetic resonance imaging (CMR) can diagnose HCM in patients where echocardiography is inconclusive, or hypertrophy is limited to areas that are poorly visualized on echocardiography, such as the anterolateral wall or apex.

Family history, morphology on imaging, response to a short period of deconditioning, and genetic testing can be used to differentiate between HCM and other conditions with LV hypertrophy including physiologic remodeling ("athlete's heart"), hypertensive heart disease, and metabolic or infiltrative storage diseases. In patients with a confirmed mutation, genetic counseling and testing of first-degree relatives is critical as mutation-positive family members may benefit from early identification and treatment, while mutation-negative family members need no further evaluation.

Intervention

All patients with HCM should be counseled to avoid particularly strenuous activity, avoid certain competitive athletics, undergo risk stratification for SCD, and have comorbid ASCVD risk factors managed according to current guidelines since comorbid coronary disease significantly reduces survival in HCM patients. All asymptomatic patients should receive an annual clinical evaluation. Asymptomatic patients with obstructive physiology should maintain proper hydration while avoiding vasodilators, high-dose diuretics, and environmental situations which may cause vasodilation.

Non-vasodilating beta-blockade is the first-line treatment for symptomatic patients since the negative inotropic and chronotropic effects decrease outflow obstruction through increased diastolic filling time and decreased filling pressures. Patients without obstructive physiology who also have a reduced ejection fraction (EF <50%) should be managed according to the current HF guidelines. End-stage HCM may present as a dilated cardiomyopathy. Patients without obstruction who have a preserved EF and remain symptomatic after, or do not tolerate, beta-blockade may be managed with verapamil, diltiazem, diuretics, ACE-I, or ARB.

For symptomatic patients with obstruction, negative inotropic agents other than beta-blockers may be used with caution since the vasodilating properties of verapamil and diltiazem may lead to decreased filling, increased obstruction, and sudden death in patients with severe obstruction. Oral disopyramide may be added to a beta-blocker or verapamil if symptoms persist, but it should not be used as monotherapy. If medical management fails, surgical myectomy by experienced operators achieves technical success in 90–95% of appropriately selected patients. Alcohol septal ablation can be used in patients who are not candidates for open-heart surgery.

In HCM patients with atrial fibrillation, anticoagulation with a vitamin K antagonist to an international normalized ratio (INR) of 2.0–3.0 or a direct oral anticoagulant (dabigatran, rivaroxaban, apixaban, edoxaban) is strongly recommended regardless of the patient's

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CHA_2DS_2-VASc score. Rate control may be achieved with beta-blockers, verapamil, or diltiazem with AV node ablation and pacemaker placement reserved for failures of medical management. First-line agents for rhythm control include disopyramide (with a rate control agent) or amiodarone. Catheter ablation and AV nodal ablation with pacemaker implantation remain rhythm control options in refractory cases.

Arrhythmogenic Right Ventricular Cardiomyopathy (Genetic)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is caused by a progressive replacement of the myocardium by fibrofatty tissue [14]. The disease is more common in men with a prevalence estimated as 1 in 2000–5000, and it usually demonstrates autosomal dominant transmission with variable penetrance. Mutations identified to date implicate a degenerative process of the cardiomyocyte involving the intercellular mechanical junction (desmosome). Symptoms may include palpitations (due to ventricular tachycardia [VT] of a left bundle branch block morphology), syncope, or aborted sudden death with initial presentation most likely after puberty but before 60 years of age. Sudden cardiac death occurs with an annual incidence of 0.1–3.0% in adults, and ventricular fibrillation (VF) can occur at any age.

The diagnosis is challenging and requires a high index of suspicion since there is no single gold standard test. The current highly specific criteria from an expert task force combine the results of multiple tests (echocardiography, CMR, endomyocardial biopsy, ECG, Holter, exercise stress) using major and minor criteria. Modifications to the original criteria for first-degree relatives of affected patients increased the overall sensitivity.

Treatment focuses on the prevention of sudden cardiac death. As with HCM, all affected individuals should limit strenuous activity and competitive athletic participation since this has been shown to increase the risk of life-threatening arrhythmias. Universal pre-participation screening in a region of Italy with a high prevalence of ARVC has reduced the annual incidence of SCD in young competitive athletes from 3.8 to 0.4 per 100,000. While an ICD is reasonable in patients with hemodynamically stable VT, medical therapy with beta-blockers or amiodarone can be used. An ICD is strongly recommended in patients with a history of cardiac arrest, syncope, VF, or hemodynamically unstable VT. As with HCM, oral anticoagulation is recommended for patients with ARVC and AF.

Other Genetic Cardiomyopathies

Other less common genetic cardiomyopathies include left ventricular non-compaction, conduction system disease, and the ion channelopathies (long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, and idiopathic ventricular fibrillation) [11].

Dilated Cardiomyopathy (Mixed)

Dilated cardiomyopathy (DCM) is characterized by an increase in LV volume with an associated reduction in LVEF that is not caused by another cardiovascular condition [15]. The previously estimated prevalence of 1 in 2700 may have underestimated the true disease burden by an order of magnitude, and DCM could be twice as common as HCM. Up to 48% of patients currently diagnosed with idiopathic DCM likely have a familial cardiomyopathy. The DCM phenotype is seen in other primary and secondary cardiomyopathies, particularly in their end stage, but these etiologies are no longer considered primary DCM. Some of the causes previously classified as DCM include myocarditis, infiltrative disease (amyloidosis, sarcoidosis, hemochromatosis), peripartum cardiomyopathy, HIV, connective tissue disease, substance abuse (alcohol, cocaine), and doxorubicin administration. HF caused by ASCVD, valvular heart disease, systemic hypertension, and congenital heart disease may also share the

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DCM phenotype. While the DCM phenotype as a whole has a poor prognosis, with 25% mortality at 1 year and 50% mortality at 5 years, truly idiopathic DCM appears to have a better prognosis than many of the secondary cardiomyopathies with less than 50% mortality at 10 years.

Patients with DCM often present with generalized symptoms of fatigue and dyspnea worsening over months to years. The classic HF symptoms of orthopnea and paroxysmal nocturnal dyspnea are also common. Physical examination reveals pulmonary and, less often, systemic venous congestion. Laboratory tests are recommended to identify other cardiovascular conditions or systemic diseases which may result in the DCM phenotype. The ECG may be normal but often shows T wave changes, septal Q waves, atrioventricular conduction abnormalities, and bundle branch blocks. Sinus tachycardia and supraventricular dysrhythmias are common, especially atrial fibrillation, while non-sustained ventricular tachycardia occurs in 20–30%. Echocardiogram with Doppler imaging is still the first-line test for diagnosis. As in HCM, CMR provides imaging of the entire myocardium while still assessing valvular regurgitation, dyssynchrony, and even ischemia when combined with late gadolinium contrast. Treatment for DCM should adhere to the current evidence-based guidelines for the management of HF as discussed in ▶ Chap. 83, "Heart Failure."

Primary Restrictive Nonhypertrophied Cardiomyopathy (Mixed)

Severe diastolic dysfunction is the hallmark of the restrictive cardiomyopathy (RCM) phenotype; LV size, shape, and systolic function are either normal or nearly so [16]. This phenotype may be seen in both HCM and hypertensive HF as well as many secondary cardiomyopathies. These include infiltrative diseases such as hemochromatosis and amyloidosis (the most common systemic cause of RCM), scleroderma, carcinoid, sarcoidosis, radiation therapy, and anthracycline use. Primary restrictive nonhypertrophied cardiomyopathy, or idiopathic RCM, is the least common etiology and occurs both sporadically and in familial forms [11].

The pathophysiology is characterized by decreased cardiac output, increased jugular venous pressure, and pulmonary congestion [16]. Biatrial enlargement accounts for an increased incidence of atrial fibrillation and frequent thromboembolic events. Both right- and left-sided HF symptoms are common presenting scenarios. Examination reveals increased jugular venous pulse and decreased pulse pressure. An S_3 gallop due to abrupt cessation of early rapid filling is common. Echocardiography is essential to rule out other causes of the patient's symptoms and to assess filling rates and pressures. The myocardium may also demonstrate patterns on echocardiography that are suggestive of a specific secondary etiology. CMR or even biopsy may be necessary in some cases to distinguish RCM from constrictive pericarditis.

Treatment with diuretics is indicated for congestive symptoms, and beta-blockers may also help with symptom control as described in HFrEF management guidelines. Transplantation is considered in refractory cases, and there may be less chance of recurrence with idiopathic RCM compared to the secondary cardiomyopathies.

Myocarditis (Acquired)

Myocarditis is an inflammatory disease of the heart muscle [17]. The gold standard diagnosis is by histologic and immunologic criteria from endomyocardial biopsy (EMB); however, the diagnosis is often made clinically. Due to the discrepancies in diagnosis, the true incidence of myocarditis is difficult to estimate. It affects children and adults, but it is more common in younger patients. Myocarditis may be caused by infections (most commonly viral), autoimmune disease, medications, and toxins (Table 8). There is significant geographical variation with parvovirus B19 and human herpes virus-6 extremely common in some areas, while coxsackievirus type B remains common in other regions [18].

The inflammation of myocarditis is first caused by either direct microbial damage or toxic damage

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Table 8 Etiologies of myocarditis

Infection		
Bacteria	Staphylococcus, streptococcus, pneumococcus, meningococcus, gonococcus, salmonella, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, mycobacterium, *Mycoplasma pneumonia*, brucella	Diphtheria is a common cause in areas without adequate vaccination
Spirochetes and rickettsia	Borrelia (Lyme disease), leptospira, *Coxiella burnetii* (Q fever), *Rickettsia rickettsii* (Rocky Mountain spotted fever), *Orientia tsutsugamushi* (scrub typhus)	Patients with Lyme myocarditis can be co-infected with *Ehrlichia* or babesia
Fungi	Aspergillus, actinomyces, *Blastomyces*, candida, *Coccidioides*, cryptococcus, histoplasma, mucormycoses, nocardia, sporothrix	
Protozoans and parasites	*Trypanosoma cruzi*, *Toxoplasma gondii*, *Entamoeba*, leishmania, *Trichinella spiralis*, *Echinococcus granulosus*, *Taenia solium*	*Trypanosoma cruzi* (Chagas disease) is a common cause in Central and South America, may also have bundle branch block
Viruses	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, respiratory syncytial virus, mumps virus, measles virus, rubella virus, hepatitis B virus, dengue virus, yellow fever virus, chikungunya virus, Junin virus, Lassa fever virus, rabies virus, human immunodeficiency virus-1 (HIV)	Viral myocarditis is the most common cause in the developed world Myocarditis is found in autopsies of more than 50% of patients with HIV (may also be due to antiviral medications)
	DNA viruses: Adenovirus, parvovirus B19, cytomegalovirus, human herpesvirus 6, Epstein-Barr virus, varicella zoster virus, herpes simplex virus, variola virus, vaccinia virus	
Autoimmune/immune-mediated disease		
Allergens	Tetanus toxoid, vaccines, serum sickness	
	Drugs: Penicillin, cefaclor, colchicine, furosemide, isoniazid, lidocaine, tetracycline, sulfonamides, phenytoin, phenylbutazone, methyldopa, thiazides, amitriptyline	Drug-induced hypersensitivity can improve after withdrawal of the drug; steroid treatment may be required
Alloantigens	Heart transplant rejection	
Autoantigens	Infection-negative lymphocytic myocarditis, infection-negative giant cell myocarditis	Considered idiopathic if no viruses are found on EMB
	Associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, Kawasaki disease, inflammatory bowel disease, scleroderma, polymyositis, myasthenia gravis, insulin-dependent diabetes mellitus, thyrotoxicosis, sarcoidosis, Wegener's granulomatosis, rheumatic heart disease (rheumatic fever)	Cardiac sarcoidosis (idiopathic granulomatous myocarditis) must have negative stains for infectious causes for diagnosis
Toxins		
Drugs	Amphetamines, anthracyclines, cocaine, cyclophosphamide, ethanol, fluorouracil, lithium, catecholamines, hemetine, interleukin 2, trastuzumab, clozapine	
Heavy metals	Copper, iron, lead	

(continued)

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Table 8 (continued)

Physical agents	Radiation, electric shock	
Misc.	Scorpion sting, snake and spider bites, bee and wasp stings, carbon monoxide, inhalants, phosphorus, arsenic, sodium azide, pheochromocytoma, beriberi	

Note: *RNA* ribonucleic acid, *DNA* deoxyribonucleic acid
Source: Caforio et al. [19], Fung [18]

[19]. Myocyte death causes the release of cytokines and activation of the immune system. This exposes antigens that are normally hidden from the immune system which induces both a cellular and humoral immune response. This immune response may resolve, as in acute myocarditis, or persist and result in chronic myocarditis. Ongoing destruction and remodeling of the myocardial tissue will eventually lead to the DCM phenotype.

Presentation and Diagnosis

Some patients have minimal symptoms and may never present to a clinician, while others have a severe course of illness and develop severe, life-threatening symptoms. The European Society of Cardiology has described four main presentations of significant acute myocarditis (Table 9). The most common presenting symptom is dyspnea, but patients will frequently report chest pain or palpitations. Because myocarditis is often caused by viral infection, the patient may report respiratory or gastrointestinal illness 1–4 weeks before symptom onset. Myocarditis should be considered as a possible diagnosis for patients presenting with any cardiac syndrome [18]. These include AMI, HF, pericarditis, arrhythmias, heart block, and SCD. Myocarditis must be excluded in a suspected case of sudden infant death syndrome. The evaluation is complicated by the fact that all of these conditions may coexist with myocarditis.

All patients suspected to have myocarditis should first be evaluated with ECG and echocardiogram. The findings of these studies in myocarditis are variable as described in Table 9. Troponin, ESR, and CRP are often elevated and should be measured. Routine viral serology is not recommended. If the initial evaluation of the patient still indicates myocarditis is likely, the patient should be managed in a center capable of hemodynamic monitoring, cardiac catheterization, and EMB. Patients will frequently require cardiac catheterization to rule out acute coronary syndrome (ACS) as the cause for their symptoms, as there is significant overlap in presentation. CMR is being used more frequently in the evaluation of myocarditis, but current evidence does not justify using it for definitive diagnosis. EMB is safe when done by an experienced clinician and can guide specific therapies.

Intervention

If the patient is hemodynamically unstable, they must be stabilized for transfer to the appropriate care team and intensive care initiated. Ventricular assist devices or extracorporeal membrane oxygenation may be used, often as a bridge to transplant. Stable patients may decompensate quickly, so at a minimum, they should be hospitalized for initial evaluation and observation [19]. All patients with HF should be treated according to current guidelines which include diuretics, beta-blockers, and ACE-I or ARB. Arrhythmias should also be managed according to current guidelines. Digoxin is not recommended as animal studies have shown that it may increase myocardial injury [17]. Temporary pacing may be required if complete heart block is present. ICDs are often not indicated until the acute phase of myocarditis has subsided, as the arrhythmia may also subside. All patients with myocarditis should avoid NSAIDs, as they may increase mortality [19]. Exercise should be avoided

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Table 9 Clinical presentation of patients with myocarditis

Clinical presentation	Diagnostic and clinical findings	Length of illness
Chest pain similar to acute MI	ST/T wave changes (ST segment elevation or depression, T wave inversion), elevated troponin (may have time course similar to acute MI or may be elevated for a prolonged period of time), no angiographic evidence of coronary artery disease	Several hours or days
New onset or worsening heart failure	Absence of CAD, no known cause of heart failure, impaired systolic function (LV or RV) seen on echocardiogram, nonspecific ECG signs, bundle branch block, AV block, and/or ventricular arrhythmias	2 weeks to 3 months
Chronic heart failure with symptoms and recurrent exacerbations	Absence of CAD, no known cause of heart failure, impaired systolic function (LV or RV) seen on echocardiogram suggestive of dilated cardiomyopathy or nonischemic cardiomyopathy, nonspecific ECG signs (see point 2 above)	More than 3 months
"Life-threatening condition" in the absence of CAD and known heart failure	Life-threatening arrhythmias and aborted sudden death, cardiogenic shock, *or* severely impaired LV function	Any duration

Note: *CAD* coronary artery disease, *LV* left ventricle, *RV* right ventricle, *ECG* electrocardiogram
Source: Caforio et al. [19], Fung [18]

until complete resolution and for at least 6 months in competitive athletes. There are no specific preventive measures for myocarditis.

Specific therapies may be indicated in certain cases, especially if an etiology is found on EMB. Antiviral treatment with ribavirin and interferon alfa has shown some benefit; however, it is most helpful early in the course of the viral illness, and myocarditis is often diagnosed too late. Interferon beta has been shown to be effective in some chronic cases. Intravenous immunoglobulin is often used, particularly in pediatric cases; however, the overall data supporting its use is inconclusive, especially for adults. Immunosuppressive therapy can play a role in some cases, especially giant cell myocarditis and chronic myocarditis with DCM unresponsive to traditional treatment. Immunosuppressive agents include cyclosporine, azathioprine, and prednisone.

Stress-Induced ("Takotsubo") Cardiomyopathy (Acquired)

Stress-induced cardiomyopathy, or apical ballooning syndrome, first described in Japan, is characterized by a ventricle which resembles an octopus trap (a takotsubo) which is triggered by acute physical or psychological stress [15]. It is more common in postmenopausal women with a presentation that mimics ACS, often with ST elevation and elevated cardiac enzymes, and is seen in 1–2% of patients undergoing angiography for ACS. Subsequent studies demonstrate no evidence of ischemia, no pheochromocytoma, and no myocarditis. The LV dysfunction often resolves within days to weeks after initial presentation.

Peripartum Cardiomyopathy (Acquired)

Peripartum cardiomyopathy (PPCM) shares the DCM phenotype and develops within the last trimester of pregnancy or first 5 months postpartum with an incidence of 1 in 300–4350 live births [15]. Risk factors include multiparity, advanced maternal age, long-term tocolysis, and African descent. It is a diagnosis of exclusion that requires no identifiable cause of HF and no history of heart disease prior to diagnosis. Many patients experience spontaneous recovery in the first 6 months after diagnosis and have an excellent prognosis; however, if cardiomegaly persists past 4–6 months, mortality increases to 50% at 6 years. PPCM can recur in subsequent pregnancies with the highest risk in patients whose LVEF has not

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normalized. GDMT for HFrEF must be adjusted if the patient is still pregnant or breastfeeding. Anticoagulation is particularly important due to a high rate of venous thromboembolism. European guidelines suggest that bromocriptine may improve outcomes in patient with severe PPCM, but this is controversial, and bromocriptine will inhibit lactation [20].

Tachycardia-Induced Cardiomyopathy (Acquired)

The severity of tachycardia-induced cardiomyopathy is correlated with the duration and rate of the inciting tachycardia [15]. Any ventricular tachycardia, frequent premature ventricular complexes, or supraventricular tachycardia with rapid ventricular response may induce this largely reversible cardiomyopathy. Treatment is directed at correcting the causative tachycardia, and subsequent improvement of the cardiomyopathy, while not guaranteed, is expected.

Pulmonary Hypertension and Cor Pulmonale

Pulmonary hypertension (PH) is a complex disease with multiple etiologies. Regardless of the underlying cause, it is defined by a mean pulmonary artery pressure >25 mmHg at rest measured by right heart catheterization (RHC) [21]. The World Health Organization (WHO) classifies PH into five groups based on etiology and pathophysiology (Table 10). All etiologies of PH are felt to

Table 10 Classification and epidemiology of pulmonary hypertension (PH)

WHO classification		Associated diseases	% of all PH cases	Others
Group 1	Pulmonary arterial hypertension (PAH)	Idiopathic (IPAH), familial, "associated with" (connective tissue disorder, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infections, drugs, and toxins), persistent pulmonary hypertension of the newborn, others	4.2%	PAH 15 cases/million adult population IPAH 5.9 cases/million adult population
Group 2	Pulmonary hypertension with left heart disease	Left-sided atrial or ventricular heart disease, left-sided valvular heart disease	78.7%	Up to 60% of with severe LV systolic dysfunction have PH Almost all patients with symptomatic mitral valve disease have PH
Group 3	Pulmonary hypertension associated with lung diseases and/or hypoxemia	Chronic obstructive pulmonary disease (COPD), interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, developmental abnormalities	9.7%	More than 50% of patients with advanced COPD have PH
Group 4	Pulmonary hypertension due to chronic thrombotic and/or embolic disease	Proximal pulmonary arteries, distal pulmonary arteries, non-thrombotic pulmonary embolism (tumor, parasites, foreign material)	0.6%	Incidence is 0.5–2% of survivors of acute pulmonary embolism
Group 5	Miscellaneous	Sarcoid, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)	6.8%	These cases cannot otherwise be classified

Note: *LV* left ventricle, *HIV* human immunodeficiency virus
Source: Galiè et al. [22] and McLaughlin et al. [24]

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have one or more underlying pathophysiologic mechanisms: vascular injury, an alteration in the balance of vasodilatation and vasoconstriction, and thrombotic changes in the pulmonary vasculature. Rarely, PH can be familial, and 70% of these cases have been associated with mutations of the BMPR2 gene [22]. The right ventricle (RV) is a low-pressure chamber with thin walls, as it normally pumps against the low resistance of the pulmonary vascular bed [23]. With the increased resistance of PH, the RV can hypertrophy and/or dilate, causing right ventricular failure (RVF). While RVF can result from any type of PH, the term "cor pulmonale" has historically been used to describe RVF secondary to diseases affecting the function or structure of the lungs, which would imply WHO group 3 disease.

Presentation and Diagnosis

The presentation of PH is very nonspecific, so the physician's challenge is to be aware of the risk factors for PH and to have an appropriate index of suspicion. The goal of the evaluation and early consultation is to identify an underlying cause, prognosis, and treatment options. The most common presenting symptoms include dyspnea (initially only with exertion), fatigue, chest pain, pre-syncope/syncope, lower extremity edema, and palpitations. Physical exam may be benign at first. With more severe PH, one may appreciate an S_3 heart sound, the holosystolic murmur of tricuspid regurgitation, or the early diastolic murmur of pulmonic regurgitation. As PH progresses, signs of RVF may develop with increased jugular venous distention, RV heave, and a prominent P2. Significant RVF may be evidenced by an S_4 heart sound, peripheral edema, hepatomegaly, and ascites.

If a patient has signs, symptoms, or history suggestive of PH, echocardiography is the next diagnostic step [21]. If there is evidence of PH, the most common causes of PH should be considered first (left heart disease, lung disease, and hypoxia; group 2 and 3 disease). A focused evaluation can include further history taking, ECG, X-ray, pulmonary function tests, blood gas analysis, polysomnography, and high-resolution computed tomography. Chest radiograph may show increased hilar structures and enlarged RV and right atrium. ECG usually reveals normal sinus rhythm with right chamber enlargement and a strain pattern. If the diagnosis of heart or lung disease is confirmed, and there are no signs of severe PH or RVF, the physician can continue with appropriate care for the underlying disease. If severe PH or RVF is present, the patient should be referred to a PH expert center for further investigation, including RHC. If heart or lung disease is not evident, the next step is to search for chronic thromboembolic pulmonary hypertension (CTEPH, group 4) with V/Q scintigraphy. This should be done even if the patient does not have a known history of pulmonary embolism, as CT pulmonary angiography may not be sensitive enough to confidently rule out group 4 disease [25]. Patients with CTEPH will also require referral and RHC. If this evaluation does not elucidate a cause of PH, broad work-up for pulmonary arterial hypertension (PAH, group 1) and miscellaneous other causes (group 5) is needed at a PH referral center.

Differential Diagnosis

CAD and cardiomyopathies leading to RVF may present with the same symptoms and signs as PH. The nonspecific presentation of the disease often results in significant diagnostic delays.

Intervention

Treatment of PH primarily focuses on supportive care and management of the underlying disease process [25]. All patients should use supplemental oxygen as needed to keep oxygen saturation $\geq$90% during rest, exercise, and sleep. If patients have RVF, it should be treated appropriately, typically with diuretics and salt restriction. Patients with CTEPH require long-term anticoagulation. These patients may also require pulmonary thromboendarterectomy, which can be curative. Pulmonary rehabilitation may be valuable for

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some patients to counter deconditioning. Patients should remain active and exercise but avoid isometric exercises which can increase risk of syncope. Female patients should be counseled to avoid pregnancy, a high-flow state that can worsen symptoms.

Several specific therapies exist for patients with PAH (WHO group 1). Vasodilator response testing should be completed during RHC to identify appropriate candidates since an empiric trial of therapy in a nonresponder can have negative hemodynamic outcomes. Pharmacologic options include calcium channel blockers, prostacyclin derivatives, endothelin receptor antagonists, and drugs that target nitric oxide pathways [26]. These group 1-specific drugs are typically not used for group 2–5 disease and may worsen outcomes in those patients. The choice of agent is based on severity of disease; oral medicines are used in lower-risk patients, while parenteral therapies are reserved for higher-risk patients. The 6-minute walk test or graded treadmill test can be used for risk stratification. The presence of RVF is a poor prognostic factor [23]. Patients with group 1 disease may also benefit from anticoagulation, typically with warfarin to an INR of 1.5–2.5. Lung transplantation may be considered in patients with group 1 disease who fail medical therapy and in group 3 patients who progress to end-stage lung disease.

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Part XVIII

The Respiratory System

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Obstructive Airway Disease

87

Timothy D. Riley and Ashley Morrison

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Asthma

General Principles

Definition/Background

Asthma is a respiratory disease characterized by chronic airway inflammation and is defined by symptoms including shortness of breath, wheeze, chest tightness and cough along with variable limitation in expiratory airflow [1]. Advances in medical therapy have greatly increased the options for treatment for patients with asthma; however it remains one of the most common major non-communicable diseases and has a substantial impact on quality of life. Adequate care of patients suffering from asthma involves the triad of systematic chronic care plans, support for self-management, and appropriate medical therapy [2].

Epidemiology

Asthma afflicts around 300 million people worldwide, ranking 16th among the leading causes of years lived with disability and 28th among the leading causes of burden of disease. While high-income countries have a higher asthma prevalence, low- to middle-income countries account for most asthma-related mortality [3]. In 2018, 7.5% of children and 7.7% of adults in the USA had been diagnosed with asthma, including 9.1% of females and 6.2% of males. Impoverished persons or those less

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than 100% of the poverty threshold are more likely to suffer from asthma (10.8%) compared to those at 450% of the poverty threshold (6.5%) [4].

Classification

Asthma may be classified as intermittent, mild persistent, moderate persistent, or severe persistent as detailed in Table 1.

There are several different clinical phenotypes of asthma that have been identified including allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity [1].

Diagnosis

The diagnosis of asthma should be based on detailed history and physical examination in combination with spirometry and/or peak expiratory flow.

History

Patients with respiratory symptoms should be asked about a history of allergies, atopic dermatitis, and symptoms starting in childhood, all of which increase the likelihood that symptoms are secondary to asthma. Family history of allergy and asthma also increase the likelihood of asthma [1].

Respiratory symptoms including wheeze, shortness of breath, cough and/or chest tightness are suggestive of asthma. Table 2 lists features that increase and decrease likelihood of asthma as a diagnosis [1].

Physical Examination

The most common abnormality on physical is expiratory wheezing; however, there are often no abnormalities detected on exam, especially if the patient is not in an acute exacerbation. Wheezing may also be caused by inhaled foreign body, tracheomalacia, or respiratory infections. Other signs on physical exam such as nasal polyps or atopic dermatitis would not be specific for asthma but suggest associated conditions such as allergy and atopy [1].

Laboratory and Imaging

Laboratory testing for specific immunoglobulin E may suggest the presence of atopy which increases the likelihood a patient that has respiratory symptoms is suffering from allergic-type asthma; however this test is not specific for asthma itself. Similarly, skin prick testing suggests the presence of atopy but is not a specific diagnostic test for asthma [1].

Table 1 Classification of asthma severity in adults and adolescents age ≥ 12 years [1]

	Intermittent	Mild persistent	Moderate persistent	Severe persistent
Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	7x/week
SABA[a] use for symptom control	≤2 days/week	>2 days/week but not daily and not more than once on any day	Daily	Several times/day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
FEV_1[a] (% predicted)	>80%	>80%	60–80%	<60%
FEV1/FVC[a]	Normal	Normal	Reduced 5%	Reduced >5%
Asthma exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year	Generally, more frequent and intense events indicate greater severity	Generally, more frequent and intense events indicate greater severity

[a]SABA, short-acting beta agonist; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity [5]

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Table 2 Characteristic symptom features of asthma [1]

Features that increase probability of asthma	Features that decrease probability of asthma
Often worse at night or early morning	Isolated cough with no other respiratory symptoms
Vary over time and in intensity	Chronic production of sputum
Symptoms are triggered by viral infections, exercise, allergen exposure, or environmental irritants	Shortness of breath associated with dizziness, lightheadedness, or peripheral tingling
Having more than one symptom of wheeze, cough, shortness of breath, chest tightness	Exercise-induced dyspnea with noise on inspiration
	Chest pain

Imaging does not play a role in diagnosis of asthma but may evaluate for other causes of respiratory symptoms such as pneumonia, congestive heart failure, lung cancer, etc.

Special Testing

Spirometry is the preferred initial test to measure presence and severity of airflow obstruction in adults [6]. Improvement of the forced expiratory volume in 1 s (FEV1) of $\geq$12% and 200 mL is suggestive of asthma.

Once a diagnosis of asthma has been made, peak expiratory flow (PEF) monitoring may be used in the short term to establish a baseline and initial response to treatment [1].

Nitrous oxide is a biological mediator that has been implicated in pathophysiology of lung diseases including asthma. Measurement of fractional nitrous oxide concentration (FE_{NO}) in exhaled breath is a quantitative method of measuring airway inflammation and can also predict corticosteroid responsiveness [7].

Bronchial provocation tests are another way to test for airflow limitation. Challenge agents include methacholine, histamine, exercise, and inhaled mannitol. These tests are moderately sensitive but not very specific for the diagnosis of asthma, as multiple chronic lung conditions can also cause abnormal results [1].

Differential Diagnosis

The differential diagnosis of asthma in adults is listed in Table 3 [6]. In children aged 6–11 who present with recurrent infections and productive cough, bronchiectasis and primary ciliary dyskinesia must be considered. A heart murmur may suggest congenital heart disease as a possible cause of symptoms. If a child presents with excessive cough and mucous production as well as gastrointestinal symptoms, cystic fibrosis should be considered [1].

Treatment

Medications/Immunizations and Chemoprophylaxis

Choice of initial treatment is based on the patient's presenting symptom severity and frequency. For those age 12 and above with infrequent asthma symptoms (less than twice a month) and with no risk factors for exacerbations, the preferred initial treatment is with as-needed low-dose inhaled corticosteroid (ICS)-formoterol, or with an ICS whenever a short-acting beta agonist (SABA) is taken. Sole prescription of SABAs is no longer recommended. If a patient presents with symptoms twice a month or more but less than daily, a daily low-dose ICS with as-needed SABA or as-needed low-dose ICS-formoterol is recommended. For patients with asthma symptoms most days or nighttime awakenings due to asthma once a week or more, it is recommended to initiate treatment with a low-dose ICS-long-acting beta agonist (LABA) as maintenance and reliever therapy, known as the single maintenance and reliever therapy (SMART) approach [8]. Maintenance-only ICS-LABA with as-needed SABA or medium-dose ICS with as-needed SABA may also be used for these patients. If a patient presents initially with severe uncontrolled asthma or in an acute exacerbation, start regular controller treatment with a high-dose ICS or medium-dose ICS-LABA and consider a short course of oral corticosteroids [1].

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Table 3 Differential diagnosis – cough and/or dyspnea [1, 12]

Chronic cough and/or dyspnea		Acute cough and/or dyspnea	
Source	Differential	Source	Differential
Pulmonary	Asthma	Pulmonary	Asthma exacerbation
	Lung cancer		Pulmonary embolism
	Interstitial lung disease		Pneumothorax
	Bronchiectasis		Pleural effusion
	Obliterative bronchiolitis	Infectious	Pneumonia
	Diffuse pan-bronchiolitis		Bronchitis/bronchiolitis
	Sarcoidosis	Cardiovascular	Congestive heart failure exacerbation
Infectious	Tuberculosis		Ischemic heart disease
	Atypical mycobacterial infections		Arrhythmia (e.g., atrial fibrillation)
Cardiovascular	Congestive heart failure	Irritants	Smoke, dust, or chemical exposure
	Ischemic heart disease		
Upper airway	Chronic allergic rhinitis		
	Upper airway cough syndrome		
Gastrointestinal	Gastroesophageal reflux		
Medications	ACE inhibitors		
Irritants	Smoke, dust, or chemical exposure		
Genetic	Cystic fibrosis		

After starting initial treatment, in most circumstances obtaining a measure of lung function with PFTs is beneficial. Review patient's response to initial therapy and consider step-down treatment after good control has been maintained for 3 months [1] (Fig. 1).

Treatment of asthma exacerbations in adults is dependent on exacerbation severity. For mild (peak expiratory flow rate [PEFR] > 75%) to moderate (PEFR 50–75%) exacerbations, outpatient management is appropriate with increased frequency of SABA or short-acting muscarinic antagonist (SAMA) use, temporarily quadrupling ICS, and systemic corticosteroids if no response to initial therapy. The recommended steroid dose is 1 mg/kg/day of prednisolone (or equivalent) per day up to 50 mg for 5–7 days. For severe exacerbations (PEFR 33–50%), management in an emergency room or urgent care facility is warranted with increased frequency of SABA or SAMA use along with systemic corticosteroids and consideration of a single dose of IV magnesium sulfate. Inpatient hospitalization is indicated if improvement is not obtained with these measures or the patient is pregnant or has one or more of the following: respiratory rate greater than 25/min, heart rate greater than 110/min, inability to speak in full sentences in one breath, or adherence concerns. For patients with life-threatening exacerbations (PEFR<33%) who may present with worsening hypoxia, hypercapnia, altered level of consciousness, hypotension, or cyanosis, treatment in an intensive care unit is required with possible noninvasive ventilation or intubation [9].

For children aged 5–11, SABA therapy is recommended to treat symptoms of intermittent asthma. Moderate or severe exacerbations due to viral respiratory infections which are common in children should be treated with a short course of oral corticosteroids, 1–2 mg/kg/day up to a maximum of 40 mg/day for 3–5 days. Daily low-dose ICS is the preferred step 2 treatment, while alternative treatment options include cromolyn, leukotriene antagonists (LTRA), nedocromil, and theophylline. For step 3 care, a low-dose ICS plus LABA, LTRA, or theophylline and medium-dose ICS are equivalent options. The preferred step 4 treatment is medium-dose ICS and LABA, and the preferred step 5 treatment is high-dose ICS and LABA. For step 6 care, oral systemic corticosteroids long term added on to high-dose ICS and LABA is preferred [1].

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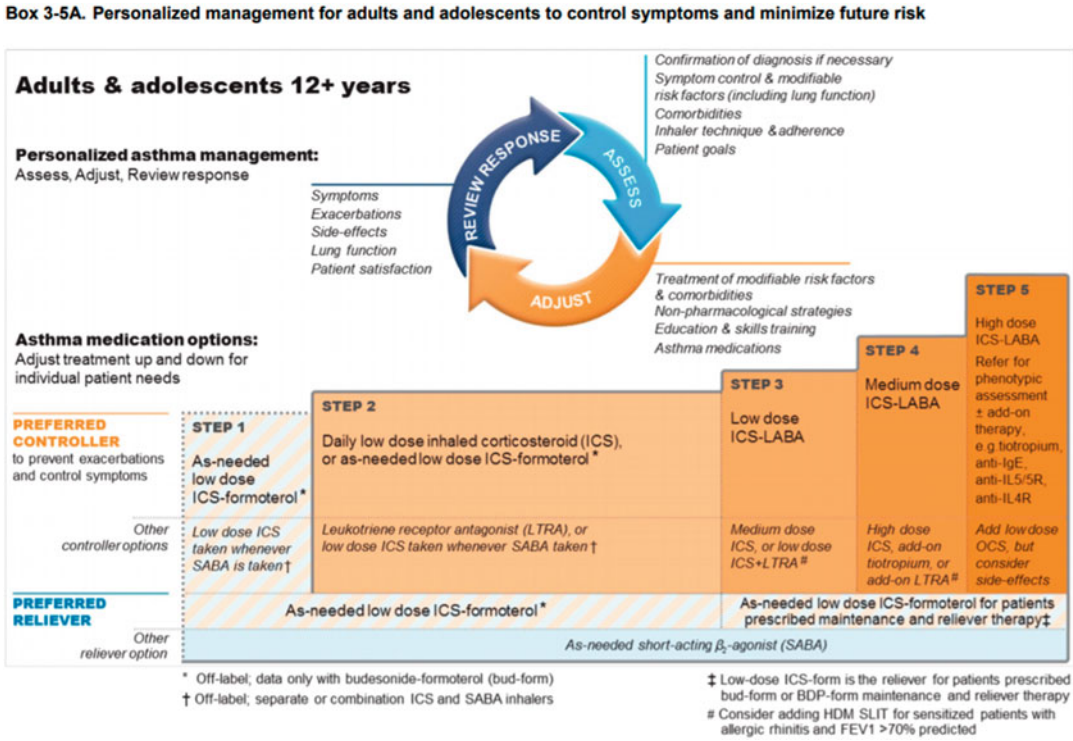


Fig. 1 Asthma management. (Reprinted with permission [1])

Referrals

In general, asthma is managed by primary care physicians, but in certain instances referral to a pulmonologist is indicated (Table 4) [6].

Counseling

Patient Education and Activation

Patient education is key in effectively managing asthma and preventing complications. A comprehensive strategy includes skills training to ensure effective use of inhalers and guided self-management with self-monitoring of symptoms or peak flow with a written action plan. For children and adolescents with asthma, a written asthma management plan should be provided for the student's school, and prompt, reliable access to medication should be ensured. Review of inhaler technique is important for all patients.

Prevention

Exposure to tobacco smoke should be eliminated if possible and those who smoke should be given cessation resources. Patients with obesity should be counseled on weight reduction strategies and distinguishing asthma symptoms from symptoms that may be due to deconditioning, mechanical restriction, or sleep apnea. Low socioeconomic status and inability to afford medications are associated with increased emergency department visits for asthma exacerbations and should be addressed [10]. Those with confirmed food allergies should be counseled on avoidance strategies and prescribed with injectable epinephrine. Allergen-specific immunotherapy may help reduce exacerbations in patients where allergy plays a significant role. Adults with asthma should be screened for occupational triggers and removed from them as soon as possible. Avoidance of indoor allergens such as mold, dust mites, and pets can be helpful in

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Table 4 Criteria for referral for asthma [6]

Unclear diagnosis	Prominent systemic features (myalgia, fever, weight loss)
Unexpected clinical findings (crackles, cyanosis, clubbing, cardiac disease)	Chronic sputum production
Unexplained restrictive spirometry	CXR shadowing
Suspected occupational asthma	Marked blood eosinophilia
Monophonic wheeze or stridor	Poor response to asthma treatment
Persistent non-variable breathlessness	Severe asthma attack

some, but these strategies can be complicated and expensive [1].

Family and Community Issues

According to epidemiological studies, approximately 21.5% of adults with asthma suffer from work-exacerbated asthma (WEA), defined as pre-existing asthma which is exacerbated by workplace conditions. WEA is associated with more symptomatic days and utilization of healthcare resources and is similar to occupational asthma in that both are associated with unemployment and loss of income. The possibility of WEA or occupational asthma should be ascertained by asking about relatedness of a patient's symptoms to the workplace [11].

Chronic Obstructive Pulmonary Disease

General Principles

Definition and Background

Chronic obstructive pulmonary disease (COPD) is a syndrome of abnormal lung physiology characterized by irreversible obstructive limitation in airflow (Fig. 2) [12]. The disease is defined by measurement through spirometry [12, 13]. Emphysema and chronic bronchitis often accompany and may be confused with COPD. Emphysema is an anatomic diagnosis, referring to destruction of alveoli. Chronic bronchitis refers to chronic cough with sputum production for at least 3 months in 2 consecutive years. Either or both of these diagnoses can occur together with or separate from COPD [12]. COPD patients may experience exacerbations, characterized by increased dyspnea, cough, and sputum production and purulence [13]. Triggers for exacerbations include viral infections, bacterial infections, and environmental causes such as pollution. Exacerbations typically last 7–10 days, but symptoms may persist for more than 8 weeks [12].

Epidemiology

COPD is common and deadly. 11.7% of the population worldwide suffered from the disease in 2010, resulting in three million deaths [12], making it the most common cause of death from chronic lung disease worldwide [14]. Cigarette smoking is the most common cause of COPD. Other tobacco smoke and secondhand smoke and smoking marijuana also increase risk [12]. Other potential causes of COPD include occupational exposure, including dust and fumes, and smoke from indoor cooking [12, 13]. Patients with asthma and chronic bronchitis are more likely to develop COPD. Alpha-1 antitrypsin deficiency is a rare genetic cause of the disease [12]. Associated conditions are listed in Table 5 [12, 13].

Classification

The 2020 Global Initiative for Chronic Lung Disease (GOLD) COPD classification system recommends a "grade (number) group (letter)" classification for each patient with COPD (Fig. 3) [12]. Symptom assessment tools include the Modified British Medical Research Council (mMRC), a brief questionnaire which assesses breathlessness and predicts future mortality risk (Table 6) [15]. The COPD Assessment Test (CAT) is more comprehensive but longer [16]. The mMRC is reproduced here for its simplicity.

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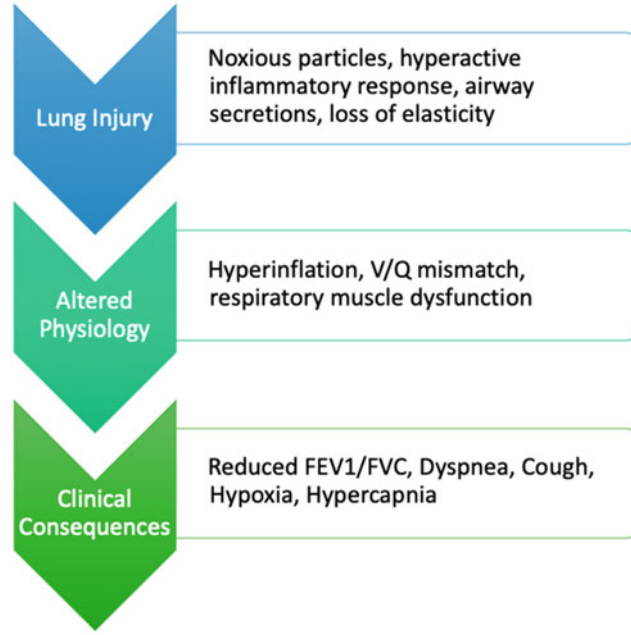


Fig. 2 Pathophysiology of COPD [12]

Table 5 Comorbid conditions with COPD [12, 13]

Condition	Examples and comments
Cardiac	Ischemic heart disease, heart failure, cardiac arrhythmias, peripheral vascular disease and hypertension
Lung cancer	Only among patients whose COPD is caused by smoking
Osteoporosis	Associated with smoking and frequent use of systemic steroids
Diabetes	Worsened by systemic steroid use
Gastroesophageal reflux disease	Associate with increased risk of exacerbations and progression
Anxiety and depression	Often underdiagnosed, associated with poor prognosis and suicidality

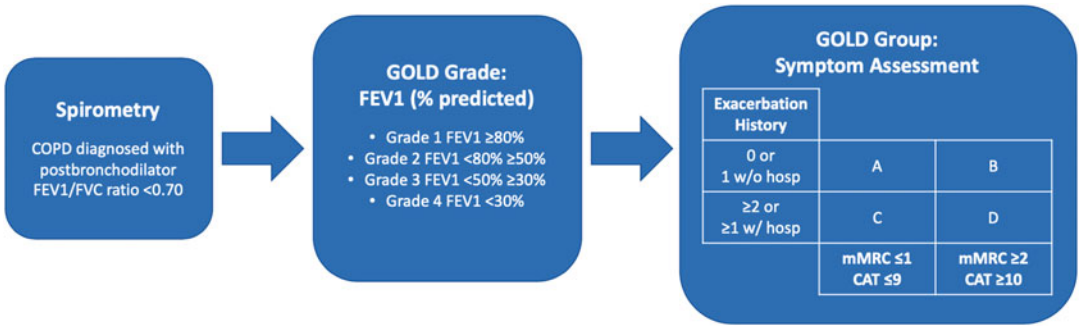


Fig. 3 GOLD 2020 classification system [1]

Exacerbations are classified as mild (requiring only short-acting bronchodilators [SABDs]), moderate (requiring SABDs with antibiotics and/or oral corticosteroids), or severe (requiring hospitalization with or without acute respiratory failure). Multiple instruments assess prognosis in COPD patients. The BODE index (body mass index, obstruction, dyspnea, and exercise

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Table 6 Modified British Medical Research Council (mMRC) Score [11]

Statement	mMRC grade
I only get breathless with strenuous exercise.	0
I get short of breath when hurrying on the level or walking up a slight hill.	1
I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	2
I stop for breath after walking about 100 meters or after a few minutes on the level.	3
I am too breathless to leave the house or I am breathless when dressing or undressing.	4

Table 7 Risk factors for COPD [1]

Modifiable	Non-modifiable
Tobacco exposure	Family history
Occupational smoke, chemical, or dust exposure	Low birth weight
Cooking or heating smoke exposure	Anatomic lung abnormalities
	Severe childhood lung infections

assessed by 6-min walk test) predicts 4-year survival [17]. The ADO index (age, dyspnea, airflow obstruction) incorporates age, mMRC, and FEV1 and predicts 3-year mortality without the 6-min walk test [13].

Diagnosis

History

The most common presentation for patient with COPD is chronic cough and dyspnea. Cough is not necessarily productive. Dyspnea is typically worse with exertion. Risk factors should be assessed (Table 7). Weight loss, fatigue, and anorexia occur later in the course of the disease [12].

Symptom severity should be assessed through the mMRC or CAT questionnaires. Patients with known COPD should be evaluated for triggers, the presence or absence of sputum as well as its volume, and healthcare utilization, particularly hospitalizations (duration, need for critical care or mechanical ventilation) [12].

Physical Examination

Physical examination has low specificity and sensitivity for diagnosis. Physical signs can include decreased breath sounds, lung hyperinflation with chest expansion, and prolonged forced expiration. With severe disease, pulmonary hypertension can result in cor pulmonale leading to leg swelling. In the context of an acute exacerbation, wheezing and rhonchi are common. The presence of rales suggests heart failure or pulmonary fibrosis [12].

Laboratory and Imaging

Complete blood count with peripheral eosinophil absolute count and percentage can help direct therapy [13]. Vitamin D levels should be checked. CRP may be useful in directing antibiotic use during exacerbations [12]. Alpha-one antitrypsin deficiency screening is recommended for all patients diagnosed with COPD [12, 13]. Chest X-ray is indicated for all nonsmokers with chronic cough who do not take ACE inhibitors [18] and may be useful in identifying comorbidities among patients with COPD [12]. Chest X-ray should also be obtained in the context of severe COPD exacerbations [12]. Chest CT is necessary prior to consideration of lung volume reduction surgery or lung transplant but is otherwise not routinely indicated [12, 13].

Special Testing

Spirometry demonstrating post-bronchodilator FEV1/FVC ratio of less than 0.70 determines the diagnosis of COPD [12]. This cutoff results in over-diagnosis in the elderly and under-diagnosis in younger patients [13]. The American Thoracic Society/European Respiratory Society guidelines recommend FEV1/FVC less than the lower limit

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of normal (LLN) as a diagnostic cutoff [19]. However, patients with FEV1/FVC greater than the LLN but less than 0.70 have worse outcomes [13]. Patients with post-bronchodilator spirometry demonstrating FEV1/FVC ratio of 0.6 to 0.8 should be repeated due to variability in test results. Spirometry should be repeated annually [12].

Oximetry is indicated with symptoms concerning for respiratory failure [12, 13]. Arterial or capillary blood gas should be considered in the setting of hypoxia to evaluate for hypercapnia. The 6-min walk test and paced shuttle walk test are standardized measures of exercise capacity [12].

Differential Diagnosis

Multiple conditions can mimic COPD. The differential diagnoses are summarized in Table 3.

Treatment

Treatment of Chronic COPD

The goals of chronic COPD treatment are to reduce symptoms, risk of exacerbations, disease progression, and death. Treatment includes behavioral techniques, medications, oxygen and ventilatory support, and surgery.

Behavioral counseling is recommended to foster understanding of disease process and progression, management of breathlessness and stress, energy conservation, and the role of the patient and provider. Counseling should include a written action plan for exacerbations. Smoking cessation can reduce progression of disease and risk of exacerbations, and other triggers should be avoided as well. Nutrition should be assessed and addressed through supplements where appropriate. Regular exercise has been shown to be beneficial. Pulmonary rehabilitation, a combination of exercise and counseling, has been shown to be highly effective at improving quality of life and exercise tolerance in patients with moderate to severe COPD (GOLD Groups B, C, and D) [12].

Multiple classes of medications are used to treat chronic COPD (Table 8); however medication treatment does not appear to change the trajectory of decreased lung function over time [12]. Medications are typically delivered through inhalers, which come in multiple formats and are frequently used inappropriately [12, 13]. Teaching and assessment of proper inhaler technique and adherence is essential. Nebulized delivery is only more effective for patients who are unable to adequately tolerate inhaler administration [12].

SABAs and SAMAs are effective for mild disease. More persistent symptoms should be treated with a long-acting muscarinic antagonist (LAMA) or LABA. If either of these classes alone are ineffective, they can be combined. Side effects of beta agonists include tremor, arrhythmia, and hypokalemia. Muscarinic antagonist side effects include dry mouth. Ipratropium has been associated with increased risk of cardiovascular events, an effect not seen to date with tiotropium. Nebulized LAMAs delivered by facemask can precipitate acute glaucoma [12].

Inhaled corticosteroids alone do not improve outcomes in patients with COPD. Combination ICS + LABA treatment has been shown to reduce the risk of exacerbations and hospitalizations in patients with moderate disease who have frequent exacerbations, particularly those with serum eosinophil counts of $\geq$300 cells/μL [12]. Eosinophil counts of $\leq$100 cells/μL are associated with poor response to inhaled corticosteroids [12, 13]. For appropriately selected patients (persistent symptoms on LAMA + LABA, with asthma or high eosinophil count), the combination of LABA, LAMA, and ICS is more effective than LABA + LAMA [20, 21]. ICS treatment is associated with hoarseness, oral thrush, bruising, and in severe COPD increased risk of pneumonia [12, 13]. Figure 4 demonstrates use of GOLD Group assignment as a guide for medication selection.

Phosphodiesterase-4 (PDE4) inhibitors work by reducing inflammation. They decrease moderate and severe exacerbations for patients with chronic bronchitis or severe COPD with an FEV1 of <50%. Side effects include diarrhea, reduced appetite, weight loss, and abdominal pain but diminish with time [12].

In patients with frequent exacerbations, azithromycin 250 milligrams per day or 500 milligrams three times a week reduce exacerbation frequency. It is less effective in smokers.

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Table 8 COPD medications[a,b]

Generic (trade)	Delivery methods	Typical adult dosing [22]
Short-acting beta agonists (SABA)		
Albuterol (Proventil, Ventolin, ProAir)	Inhaler	2 inh every 4–6 h as needed with spacer
	Nebulizer	2.5 mg every 4–6 h as needed
Levalbuterol (Xopenex)	Inhaler	2 inh every 4 h as needed with spacer
	Nebulizer	0.63 mg three times daily
Short-acting muscarinic antagonists (SAMA)		
Ipratropium (Atrovent)	Inhaler	2 inh four times daily
	Nebulizer	0.5 mg every 4–6 h
Short-acting beta agonist/short-acting muscarinic antagonist combinations		
Albuterol/ipratropium (Combivent)	Inhaler	1 inh four times daily
	Nebulizer	1 vial (3 ml) (ipratropium 0.5 mg/albuterol 2.5 mg) every 6 h
Long-acting beta agonists (LABAs)		
Arformoterol (Brovana)	Nebulizer	15 mcg twice daily
Formoterol	Inhaler (Foradil)	12 mcg every 12 h
	Nebulizer (Perforomist)	20 mcg twice daily
Indacaterol (Arcapta)	Inhaler	75 mcg (1 inh) once daily
Olodaterol (Striverdi)	Inhaler	2 inh once daily
Salmeterol (Serevent)	Inhaler	1 inh twice daily
Long-acting muscarinic antagonists (LAMAs)		
Aclidinium bromide (Tudorza Pressair)	Inhaler	400 mcg (1 inh) twice daily
Glycopyrrolate (Lonhala Magnair, Seebri Neohaler)	Inhaler	15.6 mcg (1 capsule) inhaled twice daily
	Nebulizer	25 mcg (1 vial) inhaled twice daily
Revefenacin (Yupelri)	Nebulizer	175 mcg (1 vial) once daily
Tiotropium (Spiriva)	Spiriva Respimat 2.5 mcg/actuation	5 mcg (2 inh) once daily
	Spiriva Handihaler	18 mcg (1 capsule) once daily
Umeclidinium (Incruse Ellipta)	Inhaler	62.5 mcg (1 inh) once daily
LABA/LAMA combinations		
Formoterol/aclidinium (Duaklir Pressair)	Inhaler 12 mcg/400 mcg per actuation	1 inh twice daily
Formoterol/glycopyrrolate (Bevespi Aerosphere)	Inhaler 4.8 mcg/9 mcg per actuation	2 inh twice daily
Indacaterol/glycopyrrolate (Utibron Neohaler)	Inhaler 27.5 mcg/ 15.6 mcg per capsule	1 capsule inh twice daily
Vilanterol/umeclidinium (Anoro Ellipta)	Inhaler 25 mcg/62.5 mcg per actuation	1 inh once daily
Olodaterol/tiotropium (Inspiolto Respimat)	Inhaler 2.5 mcg/2.5 mcg per actuation	2 inh once daily

(continued)

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Table 8 (continued)

Generic (trade)	Delivery methods	Typical adult dosing [22]
LABA/inhaled corticosteroid combinations		
Formoterol/budesonide (Symbicort)	Inhaler 4.5 mcg/160 mcg	2 inh twice daily
Formoterol/mometasone (Dulera)	Inhaler 5 mcg/100 mcg	2 inh twice daily
Salmeterol/fluticasone (Advair Diskus)	Inhaler 50 mcg/250 mcg	1 inh twice daily
Vilanterol/fluticasone furoate (Breo Ellipta)	Inhaler 25 mcg/100 mcg	1 inh once daily
LABA/LAMA/inhaled corticosteroid combinations		
Vilanterol/umeclidinium/fluticasone furoate (Trelegy Ellipta)	Inhaler 25 mcg/62.5 mcg/ 100 mcg	1 inh once daily
Methylxanthines		
Aminophylline	Intravenous	Loading dose: 5.7 mg/kg Maintenance dose: variable
Theophylline	Immediate release: solution Sustained release: oral pill	Immediate release: 300 mg/24 h divided q6–8h, increasing q3d to max 600 mg/24 h Sustained release (12 or 24 h formulations): 300 mg/24 h, increasing q3d to max 600 mg/24 h
Phosphodiesterase-4 Inhibitors		
Roflumilast (Daliresp)	Oral pill	250 mcg daily for 4 weeks, then 500 mcg daily
Mucolytic agents		
N-acetylcysteine (Acetadote)	Nebulized	See dosing instructions

Inh = oral inhalation
[a]Only formulations available in the USA are listed
[b]Information from Ref. [1] unless otherwise stated

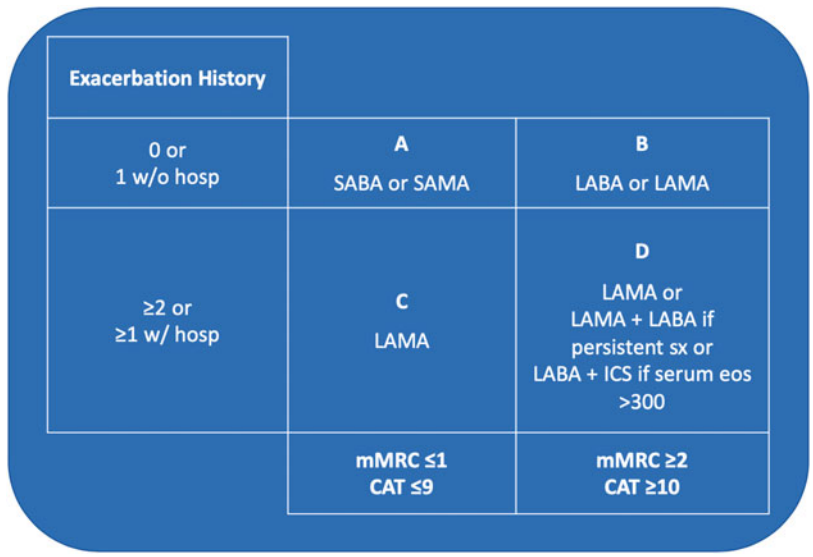


Fig. 4 GOLD Group and associated medications [1]

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Azithromycin is known to prolong the QTc interval, and frequent use can lead to antibiotic resistance as well as reversible hearing loss [12, 13].

Medications of poor or uncertain efficacy for chronic use include mucolytics, oral glucocorticoids, methylxanthines, biologics, and statins. Mucolytic N-acetylcysteine may reduce exacerbations, though which patients will benefit is uncertain, and it has not been studied in patients taking modern inhaled medications. Chronic daily oral corticosteroids are not recommended for COPD as they result in significant side effects including steroid myopathy, which reduces functional capacity and increases risk of respiratory failure [12, 13]. Methylxanthines (e.g., theophylline) act as bronchodilators and improve FEV1, but given their narrow therapeutic window and risk of life-threatening arrhythmias and seizures, they are not recommended unless other long-acting bronchodilators are unavailable [12].

Oxygen (O2) and ventilatory support can be helpful for patients with severe disease. Those with resting O2 saturation $< 89\%$ who use oxygen >15 h per day demonstrate improved survival. O2 supplementation does not improve mortality or hospitalization for patients with stable COPD and exertional hypoxemia, but it can mitigate exertional dyspnea. Hypercapnic patients discharged from the hospital may benefit from positive pressure ventilation [12].

Procedures for COPD include surgery and bronchoscopic interventions. Lung volume reduction surgery removes part of the lung to optimize ventilatory mechanics and has been shown to improve mortality for patients with severe emphysema, upper lobe emphysema, and poor post-rehab exercise capacity. It is less effective for patients with homogeneous emphysema, high exercise capacity, and decreased diffusion capacity. Bullectomy can improve dyspnea and exercise tolerance when large bullae are present. Lung transplant is indicated for patients who are not candidates for other surgeries and who have severe progressive COPD. Transplant improves health status and functional capacity but not necessarily mortality and is associated with complications including rejection, bronchiolitis obliterans, and infection. Bronchoscopic interventions include endobronchial valves, thermal ablation, and nitinol coils and have been shown to improve exercise capacity and quality of life [12].

Referral to pulmonology is appropriate for patients with persistently impaired quality of life or recurrent hospitalization despite optimized medical therapy and pulmonary rehab. Indications for hospice include disabling dyspnea and recurrent hospitalization. End of life discussion should start early due to difficulty accurately predicting prognosis. Palliative care for end-stage COPD focuses on treatment of symptoms such as dyspnea, for which effective interventions include opiates, neuromuscular electrical stimulation, chest wall vibration, oxygen, pulmonary rehabilitation, fans blowing air onto the face, and noninvasive ventilation. Benzodiazepines have not been shown to be effective. Depression, panic, anxiety, and fatigue can be improved by pulmonary rehab, cognitive behavioral therapy, and mind-body interventions [12].

Treatment of Acute COPD Exacerbations

The goals of treating COPD exacerbations include reducing severity and preventing recurrences. Indications for hospitalization are listed in Table 9. Written action plans reduce risk of hospitalization during exacerbations [12].

COPD exacerbations are treated with a combination of bronchodilators, oral corticosteroids, antibiotics, and/or oxygen and ventilatory support. Bronchodilators can be given via any available delivery method. Continuous nebulizers should be avoided. Inhalers dosed hourly for 2–3 h then every 2–4 h are recommended for acute symptoms. Combinations of SABA + SAMA are more effective than either alone. Oral corticosteroids (prednisolone [Prednisone] 40 mg daily for $\leq$5–7 days) improve rates of treatment success, reduce relapse, and improve symptoms but are associated with increased risk of pneumonia, sepsis, and death. Antibiotics for 5–7 days are indicated in COPD exacerbations featuring increased sputum purulence, but not when sputum is white or clear. Normal C-reactive protein may indicate that antibiotics are not needed [12]. First-line antibiotics include trimethoprim-sulfamethoxazole

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Table 9 Indications for hospitalization during COPD exacerbation [12, 13]

Category	Examples
Acute respiratory signs and symptoms	Resting dyspnea
	Tachypnea
	Hypoxia
	Respiratory failure
Acute central nervous system symptoms	Confusion
Failure of outpatient treatment	Persistent symptoms despite oral steroids, antibiotics, and bronchodilators
Life-threatening comorbidities	Heart failure
	New-onset arrhythmia
Inadequate social support	Lack of monitoring or transportation

(Bactrim), amoxicillin-clavulanic acid (Augmentin), macrolide such as azithromycin (Zithromax), or a tetracycline such as doxycycline (Vibramycin) [12, 13]. Patients with hypoxia should receive supplemental O2 with a goal O2 saturation between 88% and 92%. Arterial blood gases may be beneficial to monitor for CO2 retention. Noninvasive positive pressure ventilation is preferred over intubation for patients with acute respiratory failure. Intubation should be reserved for patients that are unable to tolerate noninvasive ventilation. Hospitalized patients should be monitored for fluid balance and nutrition and offered DVT prophylaxis and assistance with smoking cessation. After discharge, they should be contacted within 48 h and seen within 7 days to ensure stability. Pulmonary rehab and follow up within 3 months are recommended [12].

Prevention

Routine screening for COPD is not recommended. Smoking cessation is the most important preventative intervention and can be facilitated by counseling, pharmacotherapy, and nicotine replacement [12]. Excessive work or home exposure to dust, smoke, or pollution should be avoided. Influenza vaccination is recommended annually [12, 13]. Pneumococcal polysaccharide vaccine (PPSV23 [Pneumovax]) is recommended for all patients with COPD and all patients who smoke. Pneumococcal conjugate vaccine (PCV 13 [Prevnar]) is recommended for COPD patients age 65 or older or those who are frail or require frequent systemic steroids [13]. Vitamin D supplementation can reduce exacerbation frequency. Legislative bans can reduce smoking rates [12].

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Pulmonary Infections

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Fiona R. Prabhu, Keeley Hobart, Irvin Sulapas, and Amy Sikes

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Introduction

Pneumonia is a lung infection involving the alveoli and can be caused by a variety of microbes including bacteria, viruses, and fungi. It is the leading infectious cause of hospitalization and death in the United States [1].

Most instances of pneumonia are attributable to self-infection with one or more types of microbes that originate in the nose and mouth. In healthy individuals, typical upper airway bacterial residents such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common bacteria causing community-acquired pneumonia. Other causes of pneumonia include *Staphylococcus aureus*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Escherichia coli* that are generally seen in patients at higher risk for resistant bacteria.

In those with a serious impairment of their immune system, opportunistic microbes are more readily apparent such as fungi, viruses, and mycobacteria [1].

There are many mechanisms used by the lungs to resist infection. Physical mechanisms are structure of the upper airway, branching of the bronchial tree, sticky mucous layer lining the airways, cilia that propel mucous upward, and the cough reflex. If microbes do reach the alveoli, the immune system is usually able to destroy them [1].

A variety of strategies have been used to reduce the incidence of pneumonia. Elements of a healthy lifestyle that reduce the incidence are adequate nutrition, dental hygiene, and not smoking. For those with lung disease or impaired clearance of mucous, aerobic exercise, deep breathing maneuvers, and cough assist devices can facilitate expectoration and lung hygiene. Immunity to certain microbes can be enhanced by immunization [1].

Bacterial Pneumonia

General Principles

Definition/Background/Epidemiology

Pneumonia is a common infection in the parenchyma of the lower respiratory tract that can affect all age populations. There is significant morbidity and mortality associated with pneumonia, especially in the very young and elderly populations. Pneumonia is the leading cause of death in children younger than 5 years of age worldwide [2]. The average yearly incidence of pneumonia, specifically community-acquired pneumonia, is 5–11 per 1000, with most incident cases occurring in the winter months [3]. It is passed from person to person by viral particles on respiratory droplets.

Decisions on how to treat, whether to admit to the hospital or treat outpatient and potential prognosis, depend upon the most likely pathogen and the current clinical picture. In most cases, the pathogen is never isolated – only suspected – prior to initiation of treatment.

Classification

Pneumonia classification is based upon a variety of factors – age, clinical presentation, and comorbidities. Additionally, patients are further

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classified according to their risk factors for multidrug-resistant bacteria.

The best approach is a good history and physical exam in combination with knowledge of the most common causes of pneumonia for the presenting age patient being seen.

In 2019, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) updated the community-acquired pneumonia (CAP) guidelines [4]. Previous guidelines classified pneumonia based on the site of care (outpatient, inpatient, or ICU) and utilized terms such as healthcare-associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia. These terms have been eliminated in the new guidelines and instead base classifications solely on the severity of illness and risk factors for multidrug-resistant bacteria. The IDSA/ATS CAP severity criteria have been validated and can be used to define severe community-acquired pneumonia. Validated definition includes either one major criterion or three or more minor criteria.

2007 Infectious Diseases Society of America/ American Thoracic Society Criteria for Defining Severe Community-Acquired Pneumonia

Minor Criteria

Respiratory rate $\geq$ 30 breaths/min.
PaO_2/F_IO_2 ratio $\leq$ 250
Multilobar infiltrates
Confusion/disorientation
Uremia (blood urea nitrogen level $\geq$ 20 mg/dL)
Leukopenia (white blood cell count <4000 cells/mL)
Thrombocytopenia (platelet count <100,000 mL)
Hypothermia (core temperature < 36 °C)
Hypotension requiring aggressive fluid resuscitation

Major Criteria

Septic shock with need for vasopressors Respiratory failure

If a patient does not meet severe criteria, in general, it is safe to attempt treatment as an outpatient. The inpatient categories are then further classified by patient specific factors such as prior respiratory isolation of either MRSA or *Pseudomonas*, recent hospitalization and parenteral antibiotics (within 90 days), and locally validated risk factors for MRSA and/or *P. aeruginosa*.

In children, the suspected organism that has caused the pneumonia is based upon the age of the child: [3].

- *Birth to 3 weeks*: Group B streptococcus, *Haemophilus influenzae* type b (Hib), *Listeria monocytogenes*, and cytomegalovirus
- *3 Weeks to 3 months*: *Streptococcus pneumoniae*, *Chlamydia trachomatis*, respiratory syncytial virus (RSV) or other respiratory viruses, and *Bordetella pertussis*
- *4 Months to 4 years*: RSV and other respiratory viruses, *S. pneumoniae*, and group A streptococci
- *5–18 Years*: *S. pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*

Approach to the Patient

The most important point to consider when evaluating for pneumonia is the patient's age, the time of year, social habits, existing disease processes, travel history, or other exposure history – animals, geography, and other people. This information is best obtained from a thorough history and physical exam.

Diagnosis

History

The most common presenting symptoms in an immunologically competent patient include sudden or recent onset of:

- Cough with purulent sputum
- Dyspnea
- Fever ± chills
- Pleuritic chest pain

Other important information to obtain from the patient is with regard to recent hospitalizations, current resident location (in elderly patients), medical history, and recent medication (antibiotic) use.

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Physical Exam

Physical exam findings can vary from one patient to another, let alone one age population to another. The following exam findings are the most consistent findings in patients with pneumonia:

Vital signs:

- Temperature > 100 °F (37.8 °C)
- Tachypnea (>20 breaths/min)
- Tachycardia (>100 beats/min)
- Decreased pulse oximetry readings on room air (<92%)

General:

- Septic appearance

Respiratory exam:

- Increased tactile fremitus
- Crackles, rhonchi
- ± Egophony
- Dullness to percussion
- Decreased breath sounds/air movement

Make sure to look for red flags in patients presenting with pneumonia-type symptoms. Red flag symptoms:

- Accessory muscle use (sternal retractions)
- Grunting
- Nasal flaring
- Altered mental status
- Apnea

The presence any of these symptoms may indicate a more severe infection requiring admission to an intensive care unit.

Laboratory and Imaging

Chest radiography is the test of choice in patients with clinically suspected CAP. The presence of an infiltrate or consolidation on X-ray is required for the diagnosis of CAP (Fig. 1).

Chest radiography should be performed in:

Any patient with at least one of the following abnormal vital signs:

- Temperature > 37.8 °C (100 °F)
- Heart Rate > 100 beats/min
- Respiratory rate > 20 breaths/min

Or

Any patient with at least two of the clinical findings:

- Decreased breath sounds
- Crackles (rales)
- Absence of asthma

Routine laboratory testing is not required to establish diagnosis in an outpatient setting. Laboratory testing recommendations differ, though, for patients who are requiring admission to hospital or the intensive care unit for treatment. These include:

- Complete blood count (CBC)
- Basic metabolic panel (BMP)
- Sputum gram stain and culture
- Blood cultures drawn from two separate sites
- Arterial blood gas (ABG) if patient is experiencing respiratory distress

For patients who are being treated empirically for MRSA or *Pseudomonas*, lower respiratory tract specimens should be cultured. These specimens can come from expectorated sputum or from a bronchoalveolar lavage (BAL) [4].

Special Testing

In patients presenting with severe CAP, special testing for urinary antigens of *Streptococcus pneumoniae* and *Legionella pneumoniae* serogroup 1 has been approved [6]. Recent guidelines, however, recommend against urinary antigen testing for *Streptococcus pneumoniae* and *Legionella* [4].

Differential Diagnosis

The following might be considered in the differential based upon the patient's signs, symptoms, and comorbidities:

- Influenza
- Viral pneumonia

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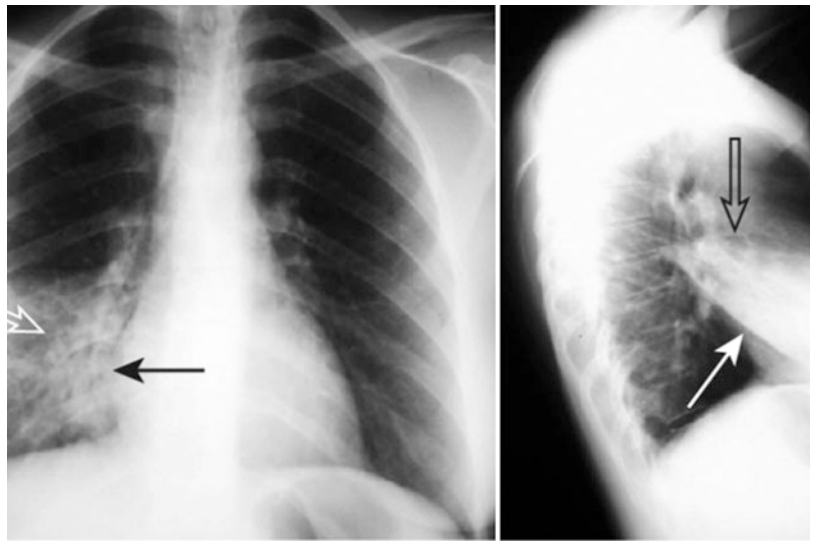


Fig. 1 X-ray of infiltrates in pneumonia [7]

- Atypical pneumonia
- Acute bronchitis
- COPD exacerbation
- Congestive heart failure (CHF)
- Pleural effusion
- Pulmonary embolism

Treatment

Medications

Severity of illness is the most important first determination to make in treatment for a patient with pneumonia; this should direct the "site-of-care" decision (hospital vs. outpatient, ICU vs. medical ward). Two scoring systems for assisting with the decision on hospitalization are the pneumonia severity index (PSI) and the CURB-65 (*c*onfusion, *u*remia, *r*espiratory rate, low *b*lood pressure, age *65* years or greater). Using one of these criteria, in addition to the clinical picture of the patient, will help guide the appropriate medication and site of treatment [4]. In the 2019 guidelines, the PSI is recommended over the CURB-65. The PSI has been shown to more consistently serve as a decision aid to increase outpatient treatment of patients with CAP and has potential to decrease unnecessary variability in admission rates, the high cost of inpatient pneumonia treatment, and the risk of hospital-acquired complications.

After deciding to admit a patient to the hospital for treatment, the next decision to be made is whether or not the patient needs ICU treatment. As mentioned, previously, according to the Infectious Diseases Society of America/American Thoracic Society, there are several clinical criteria that should be considered for ICU admission – meeting three or more of the following:

- Tachypnea, RR >25–30 breaths/min
- PaO_2 or FiO_2 ratio <250
- Multilobar infiltrates
- Altered mental status/confusion
- BUN >20 (uremia)
- White blood cell count <4000
- Thrombocytopenia, platelet count <150 k
- Temperature <36 °C
- Hypotension/septic shock requiring aggressive fluid hydration [4]

Severity of illness, presence of comorbidities and/or risk factors for MRSA or *P. aeruginosa* guides antibiotic choice for treatment. In most cases, it can be difficult to establish exact organism(s) affecting a patient; therefore, empiric antibiotic therapy guidelines have been established.

For patients who do not meet severity criteria requiring inpatient or intensive care unit admission, with or without comorbidities, treatment can be attempted outpatient. *S pneumoniae* is still the most common cause of community-acquired pneumonia and is the main target of antibiotic

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therapy. The 2019 ATS/IDSA guidelines highlight using amoxicillin as a first-line agent for outpatient CAP treatment. Previously, macrolides were recommended as first-line outpatient CAP antibiotic treatment, but increasing macrolide resistance in the United States has emerged, causing a shift away from this practice.

If attempting outpatient community-acquired pneumonia treatment in a patient with comorbidities (i.e., diabetes mellitus, alcoholism, malignancy, asplenia or chronic heart, liver, lung or renal disease), combination therapy with amoxicillin/clavulanate or cephalosporin *and* a macrolide or doxycycline *or* monotherapy with a respiratory fluoroquinolone is recommended (Table 1).

For inpatient treatment of pneumonia, the same severity criteria are applied to determine patient treatment. For nonsevere inpatient pneumonia, recommended empiric treatment is a beta-lactam + macrolide OR respiratory fluoroquinolone. For severe inpatient pneumonia, the recommended treatment would be a beta-lactam + macrolide or beta-lactam + fluoroquinolone. As the new guidelines eliminate the term healthcare-associated pneumonia, it is recommended that patients in nursing homes or with recent hospitalization only be treated for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* if they meet criteria for locally validated risk factors or antibiotic-resistant bacteria. Risk factors would include previous respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics within the last 90 days. It is also recommended that sputum and blood cultures should be ordered for any patients started empirically on anti-MRSA or antipseudomonal antibiotics to allow for more rapid de-escalation when culture findings are negative for these bacteria.

Table 1 Initial treatment strategies for outpatients with community-acquired pneumonia

	Standard regimen
No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa* (risk factors for MRSA/ *P. aeruginosa* include prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics in the last 90 days)	Amoxicillin or Doxycycline or Macrolide (if local pneumococcal resistance is <25%)
With comorbidities (such as chronic heart, lung, liver, or renal disease; diabetes mellitus, alcoholism, malignancy, or asplenia)	Combination therapy with amoxicillin/clavulanate or cephalosporin AND Macrolide or doxycycline OR Monotherapy with respiratory fluoroquinolone

Bacterial pneumonia is typically treated for a minimum of 5–14 days, with length of treatment being dependent upon degree of illness at presentation, age, comorbidities, initial response, and whether patient was hospitalized/ICU or not. Attention should be directed at monitoring length of intravenous therapy and recognizing when to switch to oral therapy. Once a patient is clinically improving and requiring no intervention to maintain hemodynamic stability, he/she can safely be switched to oral therapy to complete the course of treatment [4].

In addition to following the most updated guidelines, it is also important to be aware of local epidemiological data, as well as potential antibiotic-resistant changes with typical bacterial pneumonia treatment [5].

Patient Education

Decreasing a patient's chance of becoming ill with pneumonia is an important part of a primary care physician's job [6]:

- Counsel patients who smoke on the importance of smoking cessation.
- Encourage scheduled vaccinations.
- Educate patients on accepted hand hygiene standards: wash hands regularly with soap and warm water for at least 20 s.
- Disinfect frequently touched surfaces.
- Teach them about cough etiquette: cover the mouth and nose with a tissue when they cough or sneeze, and put used tissues in the waste basket.
- If they do not have a tissue, teach them to cough or sneeze into their upper sleeve or elbow, not their hands.

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Prevention

Immunizations

Vaccinations against preventable illnesses have long been proven effective in overall patient and population morbidity and mortality. Risk for infection with the most common bacterial pneumonia – *Streptococcus pneumoniae* – can be decreased with immunization. According to the Centers for Disease Control, the following vaccinations are important for prevention of pneumonia:

- Pneumococcal
- *Haemophilus influenzae* type b
- Pertussis (whooping cough)
- Influenza (flu) – yearly
- Measles [2, 7]

Atypical Pneumonias

Mycoplasma Pneumoniae

General Principles

M. pneumoniae is considered the most common "atypical" pathogen for community-acquired pneumonia (CAP). The prevalence of *M. pneumoniae* in adults with pneumonia can range between 1.9% and 32.5%. Outbreaks can occur in institutional settings such as schools and military bases [8]. It is usually transmitted from close person to person contact via respiratory droplets. The average incubation period is around 2–3 weeks [9], and infections tend to occur during the summer and early fall. *M. pneumoniae* pneumonia is most frequently seen among children around 5–15 years of age [10].

Approach to the Patient

Diagnosis

History and Physical

The onset of symptoms is typically gradual over the course of several days. Common symptoms include sore throat, muscle pain, headache, malaise, and chills. Patients also complain of a cough that is initially dry but becomes productive over the course of the infection. The cough is typically worse at night. Sinus pressure and otalgia can also occur. The lung exam can be normal on initial examination but can develop into scattered rales or wheezes during its progression. Extrapulmonary complications can include maculopapular rashes, arthralgia, aseptic meningitis, transverse myelopathy, and Guillain-Barré syndrome. Since the progression is gradual, a patient may not seek medical attention until a few days to a week.

Laboratory and Imaging: Special Testing

Obtaining a chest radiograph may reveal diffuse, interstitial infiltrates [10] and may be more prominent if the illness has been present for at least 2 weeks [9]. Traditionally a throat culture was obtained; however, the incubation period in a culture can take up to 3 weeks. Nuclear acid amplification testing (NAATs) is now considered the "gold standard" and has a high sensitivity and shorter turnaround time [10, 11]. A cold agglutinin test can be used as well and usually appears by the end of the first week of illness. Around 72–92% of patients with pneumonia and positive cold agglutinins (>1:32) will develop a serologic response to *M. pneumoniae*. Serology can be obtained by complement fixation (CF) or enzyme immunoassay (EIA) [8, 11].

Treatment

With the absence of a cell wall, *Mycoplasma pneumoniae* is typically resistant to glycopeptides, fosfomycin, and beta-lactam antimicrobials. Macrolides (erythromycin, azithromycin), tetracyclines (doxycycline), and fluoroquinolones (levofloxacin, moxifloxacin) are the typical therapies used to treat *M. pneumoniae*. If central nervous system involvement is suspected, consider the use of tetracyclines. In a patient with an impaired immune system and a suspicion of a systemic infection outside the respiratory system, consider the use of a fluoroquinolone [11]. Macrolides, particularly azithromycin, tend to be the most active against *M. pneumoniae* in in vitro studies [8]. The duration of antibiotic treatment is typically 5 days of azithromycin or 7–14 days with a tetracycline or fluoroquinolone.

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Prevention
Use of appropriate hand hygiene and cough etiquette.

Chlamydial Infection

General Principles

Chlamydia is a set of gram-negative obligate intracellular organisms. It includes *Chlamydia trachomatis*, *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*, and *Chlamydophila psittaci. C. trachomatis* generally presents as a genital tract or ocular infection, but the latter two can present itself as an atypical pneumonia. Around 10% of cases of community-acquired pneumonia (CAP) are related to *C. pneumoniae* [12].

Approach to the Patient

Diagnosis

History and Physical
Along with other atypical pneumonias, patients can present with productive cough, sore throat [13], sinus congestion, and malaise.

Patients who have psittacosis, caused by *C. psittaci*, tend to have a history with exposure to infected birds, which is also known as parrot fever, ornithosis or avian chlamydiosis [14]. *C. psittaci* comprises around 1% of all community-acquired pneumonia cases, and less than 50 cases a year of psittacosis are reports in the United States [14, 15]. It often presents in young to middle-aged adults. Symptoms include abrupt fever, headache, dry cough, myalgia, and malaise.

Laboratory and Imaging: Special Testing
Chest radiographs may show infiltrates. For diagnosis, oropharyngeal swabs can be used to culture *Chlamydophila* species. Serology tests, EIA, and polymerase chain reaction (PCR) can be used as well [13]. Laboratory testing may show abnormal liver enzymes, hyponatremia, elevated BUN/creatinine levels, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The patient may also have a normal white blood cell count with a "left shift" [14]. A chest radiograph can reveal interstitial or lobar infiltrates [16]. As with *C. pneumoniae*, *C. psittaci* can be diagnosed with serologic testing.

Treatment
Tetracyclines such as doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times per day) for 7–10 days are the treatment of choice for both *C. pneumoniae* and *C. psittaci* [14]. Macrolides (azithromycin) can be used as well and are usually the choice for empiric treatment for atypical pneumonia [13, 16]. For children, macrolides are the treatment of choice.

Prevention
Counsel patients about the importance of hand hygiene and cough etiquette [17].

Viral Pneumonia

General Principles

Worldwide, 900,000 children aged less than 5 years die from pneumonia every year. Despite advances, a cause is not always ascertained in a patient with pneumonia. Recent prospective pneumonia etiology studies have failed to detect a pathogen in greater than 50% of adults and approximately 20% of children hospitalized with pneumonia. In these same studies, viruses were more commonly detected than bacteria in both adults and children, accounting for greater than 25% of detections in adults and greater than 70% in children [18].

Epidemiology

More studies are showing that viral pathogens are an important cause of community-acquired pneumonia (CAP), including viruses other than influenza. In a large epidemiological study conducted by the Centers for Disease Control and Prevention despite an extensive diagnostic workup performed, no pathogen was detected in 62% of cases, vital pathogen was detected as the single pathogen in 22% of cases, bacterial pathogens were detected in 11% of cases, and co-infection virus-bacteria were detected in 3% of cases.

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Among the viral pathogens, human rhinovirus was the most commonly detected followed by influenza virus [19].

In the EPIC (Etiology of Pneumonia in the Community) study among the 2222 children with pneumonia, the most commonly detected viruses were respiratory syncytial virus (28%), human rhinoviruses (27%), human metapneumovirus (13%), adenoviruses (11%), parainfluenza 1 to 3 viruses (7%), influenza A and B viruses (7%), and coronaviruses (CoV, 5%) [18].

As of the time of writing this chapter, there has been a declaration of a pandemic with COVID-19 which is part of the group of coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Coronaviruses are single-stranded RNA viruses, and there are six that have been identified in humans. In SARS, nosocomial transmission was an important factor in epidemic spread. In MERS, direct contact with dromedaries in the 2 weeks before illness onset was a strong association [20].

Transmission

For influenza and RSV, droplet and fomite transmission are the most common methods of transmission.

Influenza has an incubation period of 1–3 days, and viral shedding begins before the appearance of symptoms and within the first 24 h of inoculation. Viral shedding peaks on the second day and in healthy adults is no longer detectable 6–10 days later. In children and immunocompromised adults, prolonged viral shedding occurs up to 21 days [21]. RSV viral shedding has a mean of 6.7 days with a range of up to 21 days [22].

Approach to Patient

Diagnosis

History

Infants with RSV initially present with rhinorrhea and decreased appetite followed by a cough within 1–3 days. Soon after the cough, sneezing, fever, and wheezing occur. In very young infants, the only symptoms may be irritability, decreased activity, and apnea [22].

In adults the presentation is similar to that of community-acquired pneumonia, but they may have symptoms of an upper respiratory infection for less than 5 days prior. The symptoms of an upper respiratory infection are rhinorrhea, sore throat, cough, headache, fatigue, and fever [6].

Physical Examination

The physical examination should target the following areas: general appearance and vital signs, head, eyes, ears, nose, and throat, cardiac, and pulmonary and thorax.

General appearance and vital signs are important in discerning the severity of illness. Is the patient lethargic or confused? Is the patient tachycardic or hypotensive? These are signs of more severe illness and most likely will require hospitalization.

Examination of the head, eyes, ears, nose, and throat can provide evidence for a preceding upper respiratory infection which would indicate a more viral etiology.

On cardiac examination, if there is a new gallop or murmur, then that can indicate increased severity of illness.

Pulmonary and thorax examinations are done to look for abnormal breath sounds and evidence of a consolidation or effusion which again can indicate a higher level of severity (Table 2) [6].

Treatment

Medications are given based on etiology of viral pneumonia. Influenza is treated with oseltamivir (although peramivir can also be used) [19].

Herpes simplex and varicella zoster are treated with acyclovir. No antiviral treatment of proven value is available for other viral pneumonias, and a high clinical suspicion for bacterial superinfection should be maintained. For RSV infection, high-risk infants and young children likely to benefit from immunoprophylaxis based on gestational age, certain underlying medical

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Table 2 Laboratory and imaging recommendations for viral pneumonia [23]

Office-based	
RSV	Antigen detection test supplemented by cell culture Sensitivity of antigen detection tests range from 80% to 90% and is reliable in young children Real-time polymerase chain reaction (RT-PCR) assays are more sensitive in older children and adults who may have a lower viral load
Influenza	Rapid influenza diagnostic tests Sensitivity tests range from 50% to 70% and specificity tests range from 90% to 95%
Hospital-based	
Serology	Complete blood count with differential – To assess severity of infection Electrolytes – To assess hydration, kidney function, and glucose Blood culture for bacterial pathogens
Sputum	Culture and sensitivity for bacterial pathogens
Nasopharyngeal	For RSV and influenza
Chest X-ray	Initially, to assess for presence of consolidation or effusion
CT of chest	For those not responding to initial therapy
Specialized testing	
Serology	Titers for acute and convalescent phase – More important for seroprevalence and epidemiological studies

conditions, and RSV seasonality, palivizumab is available. This is a monoclonal antibody given in monthly intramuscular injections during RSV season [23]. In immunocompromised patients, ribavirin has been used anecdotally for severe parainfluenza and human metapneumovirus infections; cidofovir for severe adenovirus infection in both immunocompromised and immunocompetent patients; and ganciclovir in CMV pneumonitis [19].

For coronoviruses, symptomatic and supportive care are, again, the mainstay of therapy. The most commonly prescribed antiviral regimens in the clinical settings are ribavirin, interferons, and lopinavir/ritonavir [20].

Family and Community Issues

Prevention using standard precautions and droplet precautions for at least 5 days is recommended. Wash hands frequently and correctly with soap and water for at least 20 s, or use alcohol-based hand gels. Use respiratory hygiene measures such as masks or tissues to cover the mouth for patients with respiratory illness. Avoid sharing cups and utensils. Clean contaminated surfaces.

Yearly influenza vaccination is recommended, and for those whom vaccination is contraindicated, antiviral chemoprophylaxis is recommended. Encourage patients to alert providers when they present for a visit and have symptoms of respiratory infection [22, 21].

Tuberculosis

General Principles

Definition

Tuberculosis is caused by *Mycobacterium tuberculosis* (MTB). This is a large nonmotile rod-shaped obligate aerobic bacterium requiring oxygen for survival. It is commonly introduced to the body through inhalation of droplet nuclei. MTB is usually found in well-aerated upper lobes of the lungs. MTB is a facultative intracellular parasite that is engulfed by macrophages. MTB is released into the alveoli upon death of the macrophage, and the health of the host's immune system is the key factor in expression of TB disease [24].

Epidemiology

One-third of the world's populations is infected with tuberculosis (TB). In 2012, nearly nine million people around the world became sick with TB disease, and there were approximately 1.3 million TB-related deaths worldwide. TB is a leading killer of people who are HIV-infected. A total of 8920 TB cases (or 2.8 per 100,000 persons) were reported in the United States in 2019 [25]. Up to 13 million people in the United States are living with latent TB infection [25].

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Classification

MTB may be cleared by the host immune system or may progress to latent TB infection or to primary TB. Latent tuberculosis infection (LTBI) means that the host immune system has used the cellular immune system mediated by T-helper cells to contain MTB in a granuloma. 5–10% of persons with LTBI are at risk of progressing to active TB disease. Immunocompromised persons (HIV, cancer, on immunosuppressing medications) are at greater risk for progression to active TB disease [24].

Approach to the Patient

Diagnosis

Screening

The Centers for Disease Control (CDC) recommends that high-risk populations be screened for latent infection. This includes HIV patients, IV drug users, healthcare workers who serve high-risk populations, and contacts of individuals with pulmonary tuberculosis. A validated risk assessment questionnaire may be used to identify children who are likely to benefit from screening.

History/Physical Examination

Classic clinical features of pulmonary tuberculosis include chronic cough, sputum production, appetite loss, weight loss, fever, night sweats, and hemoptysis. Extrapulmonary tuberculosis occurs in 10–42% of patients. In HIV-infected persons, the risk of active tuberculosis increases soon after infection with HIV. Those with a CD4 count of less than 200 cells/mm^3 may have an atypical presentation of tuberculosis with subtle infiltrates, pleural effusion, hilar lymphadenopathy, and other forms of extrapulmonary tuberculosis. At CD4 counts of less than 75 cells/mm^3, pulmonary findings may be absent, and disseminated tuberculosis is more frequent. Disseminated tuberculosis presents as a nonspecific chronic febrile illness with widespread organ involvement [24].

Laboratory/Imaging

Latent infection is diagnosed using the tuberculin skin test (TST) or interferon-gamma release assay (IGRA).

In the TST a small amount of tuberculin is injected into the dermis of the skin creating a small, pale bump. In 2–3 days the TST must be read by a trained healthcare worker. A positive reaction is induration measured in millimeters. Those people who have previously been vaccinated with bacillus Calmette-Guérin (BCG) may have a false-positive TST [26]. IGRA measures a person's immune reactivity to MTB. White blood cells from most persons infected with MTB will release interferon-gamma when mixed with antigens derived from MTB. IGRA requires a single patient visit and results can be available within 24 h. Vaccination with BCG does not cause a false-positive IGRA test. However, IGRA is more expensive than TST [26].

Active tuberculosis infection is diagnosed using sputum microscopy and culture along with chest radiography. Three sputum samples are obtained for acid-fast bacilli (AFB). In addition a nucleic acid amplification test (NAAT), a complete blood count, and electrolytes are also ordered. Sputum culture is more sensitive than smear staining, facilitates identification of the mycobacterium species by nucleic acid amplification, and evaluates drug sensitivity. Cultures may take 4–8 weeks [26]. 40–50% of TB cases are AFB smear negative and 15–20% have negative cultures [26]. Chest X-ray is often normal but hilar adenopathy is the most common abnormality found in as much as 65% of cases. Hilar changes can occur 1–8 weeks after skin test conversion. The findings often resolve within the first year of detecting a positive skin test for primary TB [24]. Pleural effusions are also common in active TB infection.

Treatment

Treatment depends on whether latent or active infection is diagnosed.

Latent infection is treated with isoniazid 300 mg daily for at least 6 months and preferably for 9 months. Alternative treatment regimens are listed on the Centers for Disease Control and

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Prevention website. All treatment regimens require directly observed therapy – a person employed by the state health department administers and ensures that the patient diagnosed with latent infection takes their medication [27].

Active drug-susceptible TB is treated with a four-drug regimen: isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). There is an intensive phase of treatment for 2 months followed by a continuation phase of either 4 or 7 months for a total of 6 to 9 months of treatment. There are four different regimens recommended by the Centers for Disease Control. The 4-month continuation phase is used in most patients. The 7-month continuation phase is recommended for the following groups: those with cavitary pulmonary TB and the sputum culture obtained at 2 months of treatment which is positive; those whose intensive phase of treatment did not include PZA; patients with HIV who are not receiving antiretroviral treatment during TB treatment; and patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the completion of the intensive phase is positive.

Pyridoxine supplementation is recommended to prevent isoniazid-induced neuropathy [27]. If there is multidrug-resistant disease, then initial treatment is based on local disease patterns and pending drug-susceptibility results; later-generation fluoroquinolones are preferred (e.g., moxifloxacin or levofloxacin) [27].

For those with active TB, sputum analysis should be done weekly until sputum conversion is documented. Patients who receive pyrazinamide should undergo baseline and periodic serum uric acid assessments. Those who receive long-term ethambutol therapy should undergo baseline and periodic visual acuity and red-green color perception testing. Also patients should be monitored for toxicity with baseline and periodic liver enzymes, complete blood cell count, and serum creatinine [27].

Drug-resistant TB is caused by TB bacteria that are resistant to at least one first-line anti-TB drug. Multidrug-resistant TB is resistant to more than one anti-TB drug and at least INH and RIF. Extensively drug-resistant TB is a rare type of multidrug-resistant TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone, and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Extensively drug-resistant TB is of special concern for people with HIV infection or other conditions that can weaken the immune system [27].

Causes of multidrug-resistant TB include drugs used to treat TB that are misused or mismanaged (e.g., people do not complete a full course of TB treatment); healthcare providers prescribe the wrong treatment (wrong dose or length of time); drugs for proper treatment are not available; drugs are of poor quality [27].

Family and Community Issues

Tuberculosis is required to be reported to local public health authorities. For control of pulmonary tuberculosis, control of infectivity is most efficiently achieved through prompt specific drug treatment. It takes 2–4 weeks for vital organisms to disappear in the sputum and 4–8 weeks to be cleared in the sputum.

Patients with sputum smear-positive TB who live in congregate settings should be placed in an airborne infection isolation room with negative pressure ventilation. Patients should cover their nose and mouth while sneezing. Persons entering rooms where TB patients reside should wear personal respiratory protective devices capable of filtering particles less than 1 micromillimeter in diameter. Patients whose sputum is negative for bacteria and who do not cough and who are known to be on adequate drug treatment do not require isolation. Handwashing and good housekeeping practices must be maintained according to policy [17].

Histoplasmosis

General Principles

Definition/Background and Epidemiology

Histoplasmosis is a pulmonary infection caused by *Histoplasma* – a fungus found in soil with large amounts of bird and bat guano [28]. People

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acquire histoplasmosis after breathing in the microconidia (microspores) from the air, often after participating in activities that disturb the soil. Although most people who breathe in the spores become mildly ill, moderate infection may present with a fever, cough, and/or fatigue. Not every person infected with this spore becomes ill; but in patients with weakened immune systems, the infection can become severe, especially if it becomes a systemic infection [28].

Anyone is susceptible to histoplasmosis if they live or have traveled to an area where *Histoplasma* lives in the soil. In the United States, *Histoplasma* mainly lives in soil in the central and eastern states, especially in the Ohio and Mississippi River valleys. *Histoplasma* has been reported worldwide, with localized foci located in Central America, Europe, Africa, and Asia [29]. Outdoor activities often associated with this fungus include cave spelunking, mining, construction/demolition, excavation, chimney cleaning, and farming/gardening.

There are specific populations who are at higher risk for developing the severe forms of histoplasmosis. This population includes patients who have weakened immune response (HIV/AIDS, previous organ transplant, or who are on chronic immune-suppressing medications), infants, and older adults (55 and older).

Approach to the Patient

Diagnosis

History

A majority of patients either will have no symptoms or will present with subacute influenza-like symptoms – dry cough, fever, myalgias, and fatigue – possibly weeks to months after exposure. In patients with acute illness, presenting symptoms can include high fever, headache, nonproductive cough, chills, weakness, pleuritic chest pain, and fatigue. Patients who are immunocompromised are at increased risk for systemic dissemination.

For patients not living in the areas of highest incidence, travel and activity history are important factors in diagnosing this illness.

Physical Examination

In general, the physical exam findings for any acute pulmonary infection will be similar to those for bacterial pneumonia:

- Tachycardia
- Tachypnea, +/− hypoxia
- Decreased or adventitious breath sounds
- Fever >40 °C (102 °F)
- Possible septic appearance

Laboratory and Imaging

Initial presentation resembles community-acquired pneumonia; therefore, the typical lab tests and imaging are completed at that time. These include a CBC and chest X-ray. Based on initial exam and diagnostic findings alone, most patients will likely be treated for a bacterial CAP; not until the patient's condition has worsened or initial antibiotic therapy has failed will additional special testing be completed.

Chest X-ray findings with acute pulmonary histoplasmosis include patchy or diffuse reticulonodular infiltrates; CT scans show +/− mediastinal or hilar lymphadenopathy [30]. At this point, further testing with treatment plan adjustments is recommended.

Special Testing

Definitive testing for histoplasmosis requires cultured growth of the organism, but this can take 4–6 weeks. Several tests are available for diagnosis of histoplasmosis once it is considered the cause of illness. Table 3 provides a list of testing available [29, 30].

For patients who present with diffuse disease or chronic disease with cavitating lesions, HIV testing or differentiation of cause of immunocompromised state should be completed.

Differential Diagnosis

- Pneumonia – bacterial, atypical, viral
- Sarcoidosis

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Table 3 Testing methods for histoplasmosis

Diagnostic method	Comments
Antigen detection Urine Serum	Most sensitive if both urine and blood are tested Acute and chronic infection *CON*: Not as useful in immunocompromised patients – Unable to mount antibody response
Culture	Diagnostic *CON*: Takes 4–6 weeks for culture to grow

- Other pulmonary fungal infections – blastomycosis, aspergillosis, coccidioidomycosis
- Lung cancer

Treatment

Medications

Table 4 summarizes the most recent recommendations on treatment of histoplasmosis. There has been a recent change in the treatment recommendations, with increased use of itraconazole. Amphotericin B is still highly recommended for patients with severe pulmonary histoplasmosis and for immunosuppressed patients [38, 29–31].

Prevention and Patient Education

For patients who are immunocompromised, education on high-risk behavior in endemic areas – cave exploration/spelunking, for example – should be provided.

Table 4 Treatment recommendations for histoplasmosis [29]

Disease acuity	Medications
Mild to moderate	Itraconazole 200 mg orally three times a day for first 3 days and then 200 mg orally once or twice daily for 6–12 weeks
Moderate to severe	Amphotericin B (lipid formulation) 3–5 mg/kg daily IV for 1–2 weeks, followed by itraconazole 200 mg orally three times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks *Plus* Methylprednisolone 0.5–1 mg/kg daily IV for the first 1–2 weeks of therapy, in patients with ARDS[a]

[a]*ARDS* acute respiratory distress syndrome

Coccidioidomycosis

General Principles

Definition/Background and Epidemiology

Coccidioides is a dimorphic fungus that is found in the soil of the southwest region of the United States. Coccidioidomycosis is an infection caused by *Coccidioides immitis* or *Coccidioides posadasii*, and it is due to the inhalation of spores [32]. The incidence of reported coccidioidomycosis has increased, from 5.3 per 100,000 population in 1998 to 42.6 per 100,000 in 2011 [33]. The reports were from the endemic areas of Arizona, California, Nevada, New Mexico, and Utah. Due to population increases in Arizona and California, the number of infections has risen to about 150,000 per year. It is also known as "valley fever" [34], or in California, San Joaquin valley fever.

Approach to the Patient

Diagnosis

History and Physical Examination

Infection is usually acquired by inhalation of the spores and living around the endemic regions of the southwestern United States. Most commonly, coccidioidomycosis usually presents itself as a self-limiting acute or subacute community-acquired pneumonia. This can develop around 7–28 days infection. The patient can present with respiratory complaints, fatigue, or arthralgia. Around 75% of patients with primary pulmonary coccidioidomycosis develop a flu-like syndrome with fever and cough [15]. For some patients, fatigue can last from weeks to months. A few patients (0.5%) infected may develop a progressive pulmonary or disseminated infection (skin, meninges, and bones). Persons of African or Filipino descent and pregnant, diabetic, and

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immunosuppressed patients have a higher risk of extrapulmonary complications.

Obtaining an accurate travel history is important. The patient should have been exposed in a region where exposure is possible (southwestern United States). The most common symptom is a respiratory illness, particularly if it involves the lower respiratory tract (i.e., pneumonia). The severity of illness varies from a mild respiratory infection to progressive pulmonary lesions or dissemination. The diagnosis of coccidioidomycosis from other causes is difficult without further testing.

Laboratory and Imaging: Special Testing

A sputum culture growing *Coccidioides* species establishes the diagnosis; however, it could take weeks for the culture to grow. *Coccidioides* species is considered by the Centers for Disease Control (CDC) as a select agent, so there are specific guidelines to oversee its handling [35]. Usually a culture is reserved for patients who require hospitalization. For most patients in an ambulatory setting, serologic testing can be used to diagnose coccidioidomycosis. IgM and IgG anti-coccidioidal antibodies are usually the screening test of choice. In 25%–30% of cases, eosinophilia is seen on a white blood cell differential [15].The most common chest radiograph abnormality is airspace opacity (58% of patients), followed by pulmonary nodules (22.8%) and a cavitary lesion (13.2%) [36].

Treatment

If there are no risk factors or no evidence of extensive coccidioidal infection, a majority of patients do not need any antifungal medication. Follow-up visits every 3–6 months for up to 1–2 years are recommended with serial chest radiographs. This is done to document radiographic resolution or to identify extrapulmonary complications. *Coccidioides* nodules generally do not calcify, which is in contrast to histoplasmosis [15]. For patients presenting with a severe illness or have risk factors (i.e., pregnancy), it is recommended to start antifungal therapy. Common antifungals used are ketoconazole 400 mg PO (per os/by mouth) daily, fluconazole 400–800 mg by PO daily, and itraconazole 200 mg PO two to three times per day. For pregnant patients, amphotericin B deoxycholate (0.5–1.5 mg/kg intravenously daily or alternate day) or amphotericin B lipid formulation (2.0–5.0 mg/kg or greater intravenously daily) is used as the antifungal of choice. Depending on the severity, the duration of therapy can range from 3 to 6 months to years.

Prevention

Dust control measures in endemic areas such as face masks, air-conditioned cabs, and wetted soil are recommended. Concurrent disinfection of discharges and soiled surfaces and terminal cleaning must be accomplished [17].

Legionnaire's Disease

General Principles

Definition/Background

Legionnaire's disease is a waterborne, pulmonary infection caused by a gram-negative, nonspore-forming, aerobic bacterium, *Legionella pneumophila*. This pulmonary infection was coined Legionnaire after an outbreak of pneumonia that occurred in people who had attended a convention of the American Legion in Philadelphia in 1976. *Legionella* is the third most common cause of pneumonia in immunocompetent patients [35].

The bacterium, *Legionella pneumophila*, loves warm water and can be found naturally in the environment. This bacterium can live in and be spread to humans from hot tubs, cooling towers, hot water tanks, large plumbing systems, or fountains. The bacteria reside on droplets of water (vapor or mist) and are inhaled from environments containing water features as described above. The incubation period is usually 2–14 days before patients notice any symptoms.

This organism should be suspected in a patient who has had progressive pneumonia-like symptoms and is resistant to standard treatment for CAP.

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Epidemiology

Since being discovered, an estimated 8000–18,000 people are hospitalized yearly in the United States with this infection [36]. It is considered the second most common pathogen detected in cases of pneumonia requiring admission to ICUs and is the third most common cause of pneumonia in immunocompetent patients [35, 36]. In the past 10–12 years, there has been a notable increase in the number of cases reported. This infection is most often reported in the fall and summer, peaking in August [36].

Approach to the Patient

Factors to consider in a patient presenting with a pneumonia-type picture and potential diagnosis of *Legionella* are:

- Older age, >65 years of age
- Smoking status
- Male
- COPD or other chronic lung diseases
- Immunosuppressed or immunocompromised
- Lung cancer
- Diabetes mellitus

Diagnosis

Prompt diagnosis and early initiation of therapy are important for adequate treatment of Legionnaire's disease [6].

History and Physical Examination

Many symptoms are associated with Legionnaire's disease, but symptoms that are consistently reported include fever, loss of appetite, dyspnea, cough, headaches, and malaise. Some patients have reported diarrhea, confusion, phlegm, and/or blood-streaked sputum/hemoptysis. In most cases, symptoms have an abrupt start. If not recognized and treated appropriately, a mild infection can rapidly turn fatal.

Additional information to glean from a patient is recent travel history (including hotel or cruise ship stay) within 2 weeks of onset of symptoms [37].

Physical exam findings might include:

- Tachypnea, RR >20
- Temperature > 40 °C (102 °F)
- Mental status changes, confusion
- Rales on auscultation
- Relative bradycardia
- Generalized abdominal tenderness

Use of special scoring systems, like the Modified Winthrop-University Hospital Infectious Disease Division's Weighted Point System for Diagnosing Legionnaire's Disease in Adults, can be crucial in early infection to diagnose correctly for treatment of Legionnaire's disease.

Laboratory and Imaging

Chest X-rays of patients with *Legionella pneumoniae* can appear identical to X-rays from other types of bacterial pneumonia; therefore, additional testing is required. In general, if these patients are admitted to the hospital, standard blood work should be collected (CBC, BMP, blood cultures × 2, sputum culture/g stain). If *Legionella* is being suspected, there are several options in testing for this organism – the choice of test will likely be driven by what is available within the clinic or hospital laboratory.

Special Testing

When Legionnaires' disease is suspected, both a urinary antigen test and *Legionella* culture of a respiratory specimen should be ordered. The culture requires a special medium, buffered charcoal yeast extract agar (BCYE). The "gold standard" and most sensitive test is the isolation of the organisms by culture from sputum or BAL. The disadvantage to culturing *Legionella* is that it can take 5–10 days for results and is a meticulous process. Cultures can yield a sensitivity of 20–80%, with a specificity of 100% [35, 36].

A serum test has been developed utilizing immunofluorescent assay (IFA) and enzyme-linked immunosorbent assay (ELISA). These tests evaluate and aid in diagnosis when the antibody titer increases greater than fourfold [31]. The time required for adequate testing

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using this method can take up to 3–8 weeks. Sensitivity and specificity of blood serum testing are 70–100% and 100%, respectively [35, 36].

A newer test being used in hospitals is the urinary antigen test. An advantage to this test is a fast turnaround time (<1 h) allowing a shorter time from presentation to diagnosis to targeted treatment. The main disadvantage to using this test for detection of *Legionella* is that it is specific for *L. pneumophila* serogroup 1 only [36]. The urinary antigen test yields a sensitivity and specificity of 80–90% and > 99%, respectively [35, 36].

Differential Diagnosis

- Bronchitis
- Q-fever
- Acute respiratory distress syndrome
- Pneumonia – viral, atypical, bacterial
- Pleural effusion

Treatment

Medications

First-line treatment for *Legionella pneumoniae* follows the guidelines for bacterial CAP – utilizing either a respiratory fluoroquinolone or azithromycin [37, 38, 36] (Table 5).

Immunizations and Chemoprophylaxis

There are no vaccines available for prevention of *Legionella* infections.

Prevention

The most important factor in preventing infection is continued maintenance of water areas, such as hot tubs and heating/cooling water systems.

Table 5 Antimicrobial therapy for *Legionella pneumoniae*

First line	**Levofloxacin** 500 mg IV or orally every 24 h for 7 days or 750 mg IV orally every 24 h for 5 days **Azithromycin** 500 mg IV or 500 mg IV daily for 7–10 days
Second line	**Doxycycline** 100 mg orally twice daily for 5–7 days

Family and Community Issues

Awareness of outbreaks and potential contaminants should be considered when multiple cases within a community are diagnosed with *Legionella*.

Mycobacterium Avium Complex

General Principles

Definition/Background and Epidemiology

Mycobacterium avium complex (MAC) is considered to be nontuberculous mycobacteria. MAC includes several subspecies: *Mycobacterium avium* subsp. *avium*, *M. avium* subsp. *silvaticum*, *M. avium* subsp. *hominissuis*, *M. avium* subsp. *paratuberculosis*, *M. avium* subsp. *intracellulare*, *M. arosiense*, *M. chimaera*, *M. colombiense*, *M. marseillense*, *M. timonense*, *M. bouchedurhonese*, and *M. ituriense* [39].

Nontuberculous mycobacteria (NTM) are normal inhabitants of soil and water. Infections occur because their occupied habitats are shared with humans, animals, fish, and poultry. The habitats include drinking water distribution systems and household plumbing [39].

Patients who receive TNF-α blockers are susceptible to NTM infections, and MAC was the most commonly implicated [40].

Approach to the Patient

Diagnosis

History and Physical Examination

Symptoms are nonspecific. Most patients present with a chronic cough, with or without sputum production or hemoptysis, and slowly progressive fatigue or malaise. Constitutional symptoms such as weight loss, fever, and night sweats are less frequent, occurring in 30–50% of patients, and often indicate advanced disease. Physical examination would be the same as for other types of pneumonia [41].

Laboratory and Imaging

Radiographic abnormalities are more specific and generally follow two distinct patterns. The first is bronchiectasis and nodular lesions mostly

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involving the lingual and middle lobe. The second is fibrocavitary lesions that mostly involve the upper lobes and resemble pulmonary tuberculosis [41].

Differential diagnoses for cavitary lesions include pulmonary malignancy, sarcoidosis, and infections by non-mycobacterial pathogens such as fungi and *Nocardia* species [41].

Special Testing

Sputum culture is required to make the diagnosis. This can be from at least two separate expectorated sputum samples or at least one bronchial wash or lavage.

Management

Treatment regimens should consist of a rifamycin (rifampin or rifabutin), ethambutol, and a macrolide (azithromycin or clarithromycin). Therapy can be given daily or intermittently depending on the disease type and severity. Nodular bronchiectasis patterns can usually be treated by three times weekly therapy. Cavitary MAC disease involves daily three-drug therapy in addition to IM streptomycin or IM/IV amikacin usually given three times weekly [40].

Pneumocystis Pneumonia

General Principles

Definition/Background and Epidemiology

Pneumocystis pneumonia (PCP) is an opportunistic infection that occurs in immunocompromised patients, such as persons infected with the human immunodeficiency virus (HIV). Patients who are on chronic immunosuppressive therapy are also at risk [42]. Traditionally the nomenclature of the organism was *Pneumocystis carinii pneumonia* (*P. carinii* ***p***neumonia), but the name has been changed to *Pneumocystis jiroveci* to distinguish the species that affects humans. The acronym "PCP" is still used today (*Pneumocystis p*neumonia) to avoid confusion in medical literature [43]. For patients with acquired immunodeficiency syndrome (AIDS), PCP is the most common opportunistic infection, but since the introduction of highly active antiretroviral therapy (HAART), the prevalence of PCP has decreased [44]. Most HIV-associated cases of PCP occur in undiagnosed HIV patients [14].

Approach to the Patient

Diagnosis

History and Physical

Patients typically have to be in an immunocompromised state to develop *Pneumocystis* pneumonia. The risk of PCP increases as the T-helper cell count (CD4) decreases in a patient. PCP usually occurs when the CD4 count is less than 200 cells/mm^3. Symptoms can include a low-grade fever, progressive dyspnea, or a nonproductive cough. Upon physical examination, a patient may have tachycardia and tachypnea. Auscultating the lung can be within normal limits but may reveal nonspecific crackles.

Laboratory and Imaging: Special Testing

With PCP, a chest radiograph can show perihilar interstitial infiltrates, which may become more dispersed as the disease process worsens. The interstitial infiltrates may progress into bilateral consolidations [14]. One may also see lung nodules. If the chest radiograph is normal, a high-resolution computed tomography (CT) scan may show ground-glass opacification or lesions cystic in nature. For diagnosis of PCP, an induced sputum (with hypertonic saline) culture should be the initial test of choice. If the culture is negative and still suspected, bronchoscopy with bronchoalveolar lavage is indicated [43]. In the HIV-infected population, an elevated serum lactate dehydrogenase (LDH) is suggestive of PCP, with levels reaching >500 ml/dL [14].

Treatment

In not acutely ill patients with PCP (PaO2 > 70 mmHg), the treatment of choice is trimethoprim-sulfamethoxazole (TMP-SMX) 20 mg/kg PO daily in two to four divided doses

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[14]. For patients who are acutely ill (PaO2 < 70 mmHg, unable to take PO), a 3-week corticosteroid taper should be added in conjunction with TMP-SMX. The patient should take prednisone 40 mg twice daily for 5 days, followed by 40 mg daily on days 6–11, and then 20 mg daily on days 12–21. For those patients who cannot tolerate TMP-SMX, alternative regimens include oral primaquine (30 mg daily) plus clindamycin (600 mg three times daily), atovaquone 750 mg orally twice a day [45], trimethoprim (5 mg/kg orally three times daily) plus dapsone (100 mg orally daily) [46], or pentamidine 4 mg/kg intravenously daily. Glucose-6-phosphate dehydrogenase (G6PD) deficiency must be checked prior to using primaquine or dapsone [44]. The duration of treatment should be 21 days. Following therapy, it is recommended for the patient to start on PCP prophylaxis.

Prevention and Community Issues

For patients with HIV, primary prophylaxis should be started when the CD4 count is less than 200 cells/mm^3. The prophylactic treatment of choice is TMP-SMX at one tablet (single or double strength) by mouth daily. Other options can include dapsone 100 mg PO daily, atovaquone 1500 mg PO daily, or pentamidine 300 mg PO nebulized every 4 weeks. With the introduction of HAART, prophylaxis can be discontinued if the CD4 levels go above 200 cells/mm^3 [42].

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Lung Cancer

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Alap Shah and Daniel Hunter-Smith

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General Principles

In the USA, primary lung cancer is the most common cause of cancer death and, after skin cancer, the second most commonly diagnosed cancer. It is one of the leading causes of morbidity and mortality in the USA. In 2019, there were an estimated 228,150 new cases of, and 142,670 deaths from, primary lung cancer [1]. Lung cancer also imposes a large financial burden on the healthcare system, with 2018 national expenditure for diagnosis and treatment totaling $14.2 billion [2].

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However, since 1992, the rates of new cases and deaths from lung cancer in the USA has been steadily decreasing. In 1999, the age-adjusted rate of lung cancer was 71 per 100,000 Americans. By 2016, it had steadily declined to 58 per 100,000 Americans, with a concomitant decrease in death rates as well, across most ethnicities and in both genders [3]. By ethnicity, African-American men, of all subgroups, have consistently had the highest incidence and death rate over the last decade. Although the gap between African-American men and other groups has been closing, this disparity still serves as a reminder of the significance of socioeconomic factors in the incidence and death rates from lung cancer.

Prevention

Efforts at the prevention of lung cancer can be divided into two separate categories: primary prevention through risk factor modification and secondary prevention through early detection of asymptomatic disease.

Primary Prevention

The CDC has declared that reducing tobacco use is a "Winnable Battle." As the vast majority of lung cancers develop in association with cigarette smoking, the primary prevention of most lung cancers can be achieved through increased smoking cessation and decreased smoking initiation. As with other neoplastic disease, there are additional risk factors involved, including environmental and occupational exposure, nutrition, and genetic predisposition.

Cigarette Smoking

It is estimated that tobacco cigarette smoking causes 80% of the lung cancer deaths in women and 90% in men. Men and women who smoke are 23 times and 13 times more likely to develop lung cancer than men and women who do not smoke, respectively. In addition, exposure to secondhand smoke among nonsmokers increases the risk of lung cancer by 20–30% [4]. Promisingly, the overall prevalence of current smokers in the USA has been steadily decreasing: from 1965 to 2017, the percentage of current cigarette smokers decreased from 42.4% to 14.0% [5]. Among high school students, the overall prevalence has also been decreasing: from 1991 to 2015, the percentage of those who smoked a cigarette within the last 30 days decreased from 36.4% to 9.3% [6]. In 1997, the prevalence had peaked at 37.7% in high school boys and 34.7% in high school girls. It has steadily declined to current levels following the 1998 Tobacco Master Settlement Agreement, perhaps demonstrating the importance of public policy in curbing cigarette use among minors. Still, with the decline in combustible cigarette use, there has been a recent increase in the use of electronic nicotine delivery systems among both minors and adults. Their effects on long-term lung cancer risk are as of yet unknown [7].

From the public health perspective, and for the primary physician, encouraging smoking cessation and preventing smoking initiation are among the most important measures that can be taken to prevent lung cancer.

Occupational and Environmental Exposure

It is estimated that occupational carcinogen exposures are responsible for 9% to 15% of cases (approximately 20,000–34,000) of lung cancer in the USA [8]. Lung cancer is known to be associated with a vast number of workplace exposures, most notably tar and soot, heavy metals (including arsenic, chromium, and nickel), asbestos, silica, and radioactive materials. The list of occupations that involve these substances is extensive and includes mining, manufacturing, printing, painting, and ionizing radiation. Cigarette smoking has been shown to potentiate the effects of some of the occupational carcinogens. In the case of asbestos, arsenic, and radiation, the combined carcinogenic effect can be multiplicative.

Air pollution is becoming increasingly recognized as a risk factor for lung cancer. While different geographic areas have varying components of particulate air pollutants, a 2014 meta-analysis by the World Health Organization classified general outdoor air pollution as a Group 1 (highest

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risk) lung carcinogen. Indoor air pollution from burning biomass is also a well-known risk factor for lung cancer and is an issue more commonly encountered in the developing world.

Ionizing radiation is also classified as a Group 1 lung carcinogen. In the USA, approximately half of an average individual's annual ionizing radiation exposure is iatrogenic, and most of the remainder is from radon-222 exposure. About half of iatrogenic radiation is due to computed tomography (CT), and the rest is from fluoroscopy and nuclear medicine. In the USA, CT scan usage is sharply rising, and it is estimated that in 2007, 1.5–2% of all types of cancers (including lung cancer) were attributable to radiation from CT scans [9]. Non-occupational radon exposure in nonsmokers is estimated to be responsible for approximately 15,000 deaths from lung cancer annually [10]. The EPA has reported that 1 in 15 US homes has radon levels at or above the recommended levels and that lowering levels in these homes could prevent 5,000 lung cancer deaths annually.

Nutrition and Exercise

There is growing evidence that diet and exercise play a role in modifying lung cancer risk. A 2009 review found that the risk for lung cancer was 22% lower in those who ate the highest amount of cruciferous vegetables compared to those who ate a minimal amount [11]. Additionally, a 2018 World Cancer Research Fund report noted that high fruit intake consistently protected against lung cancer (in one analysis, reducing risk by 23% compared to low fruit intake) and that carotenoid-containing foods probably protect against lung cancer [12]. There was also limited evidence suggesting that non-starchy vegetables, selenium, and physical activity were protective against lung cancer, whereas red meat, processed meat, butter, and high overall fat intake were causes of lung cancer. Attempts to isolate the antioxidants thought to be responsible for the protective effects from carotenoid-containing vegetables have not been successful; high-dose vitamin A supplementation in smokers was actually associated with an increased risk of lung cancer.

The interplay of antioxidants contained within foods and the possibility that carotenoids are a marker for a healthier lifestyle rather than protective on their own create uncertainty regarding to the mechanisms of the protective effects of a healthy diet. However, the evidence clearly shows that a diet high in fruits and cruciferous vegetables, combined with physical activity, is a significant part of overall lung cancer prevention.

Genetics

The lifetime risk of being diagnosed with lung cancer in smokers is approximately 17.2% in males and 11.6% in females (compared to 1.3% and 1.4% in nonsmokers, respectively) [13]. That a majority of smokers do not develop lung cancer shows that other factors are involved in the pathogenesis of lung cancer, especially genetic susceptibility. In one study, after adjusting for smoking, age, and gender, a positive family history of lung cancer conferred an odds ratio of developing lung cancer of 1.6, with an increase to 3.6 if two or more family members had been diagnosed [14].

As with other cancers, lung carcinogenesis is a multistep process, involving DNA damage at multiple levels that ultimately causes unchecked cell proliferation. Specifically, mutations within tumor suppressor genes, DNA repair genes, and oncogenes work synergistically to promote tumor growth. Dozens of genes have been noted to have mutations in those with lung cancer, including K-*ras*, *EGFR*, and p53. Recent developments in genomic profiling allow for a million or more genetic variants to be concurrently sequenced, allowing more widespread identification of mutations that may indicate an increased risk of lung cancer. Though genetic testing is not currently used for screening in clinical practice, ongoing research may make it possible that it could one day play a major role in determining susceptibility to lung cancer.

Secondary Prevention

Efforts at secondary prevention have been geared toward early detection through imaging, as other noninvasive tests (serologic, sputum, and breath

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testing) remain in developmental stages. In 2013, the United States Preventive Services Task Force (USPSTF) recommended annual low-dose computed tomography (CT) screening for high-risk current or former smokers (those with a 30 pack-year history and who have smoked in the last 15 years) aged 55–80 years old, to detect asymptomatic disease.

This recommendation was primarily based on the National Lung Screening Trial (NLST), a landmark trial which enrolled over 53,000 patients in academic medical centers across the USA. The NLST demonstrated a 20% reduction in lung cancer mortality with annual low-dose CT compared to chest X-ray, with a number needed to screen (to prevent one death from lung cancer) of 320 [15]. The subsequent NELSON trial, which enrolled 13,000 men and 2,500 women in the Netherlands and Belgium, showed a reduction in lung cancer-specific mortality of 24% in men and 33% in women over 10 years, with a number needed to screen of 133 in men. The NELSON trial used a protocol based on lung nodule volume (as opposed to nodule diameter, used by previous studies) which significantly reduced false positives and unnecessary harms, a noted concern with the NLST findings. In addition, the NELSON trial used longer intervals between screenings, suggesting that biennial screenings may be as effective as annual screenings in select populations [16, 17].

Since the USPSTF recommendation, analyses have estimated the cost of annual low-dose CT screening to cost between $53,000 and $75,000 per quality-adjusted life-year (QALY) gained which is not dissimilar to the costs of screening mammography and colonoscopy [18].

Classifications

Lung cancer originates from cells in the respiratory epithelium (resulting in small cell lung cancer, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) and the pleura (resulting in mesothelioma). Much rarer forms of lung cancer include spindle cell carcinoma, giant cell carcinoma, and carcinosarcomas; they are classified as non-small cell lung cancers. The relative incidence of the most common types is shown (*see* Table 1) [19]. In recent decades, adenocarcinoma has become the most prevalent type of lung cancer. This may be due to the widespread use of filtered cigarettes, which allow carcinogens to travel further down the bronchial tree, bypassing protective epithelium. Smoking is associated with nearly all types of lung cancer, but is most closely associated with small cell and squamous cell cancers. In those who have never smoked, adenocarcinoma is the most common type of cancer [20].

Table 1 Incidence of Lung Cancer type by histology

Lung cancer type by histology	Incidence (%)[a]
Small cell lung cancer (SCLC)	18%
Non-small cell lung cancer (NSCLC)	74%
Adenocarcinoma	46%
Squamous cell carcinoma	25%
Large cell carcinoma	8%
Mesothelioma	<0.02%

[a]Due to a combination of sources, the total may not add up to 100%

The stage of disease is the strongest predictor of survival, though histology also plays an important part in prognosis [21]. Among the major histological types, adenocarcinoma generally has the highest 5-year survival, and small cell has the poorest survival. For localized disease, the 5-year survival is approximately 69% for adenocarcinoma, 46% for squamous cell, 48% for large cell, and 27% for small cell. For regional disease, the survival drops to 42% for adenocarcinoma, 26% for squamous cell, 29% for large cell, and 15% for small cell. With the new implementation of screening CT for lung cancer, cancers may be detected at earlier (more local) stages, which may improve survival and increase the amount of disease amenable to a cure.

Diagnosis

Clinical Presentation

The clinical presentation of a lung cancer is driven by the site of origin and the extent of the disease. It is not uncommon for it to be an asymptomatic finding

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on a chest X-ray or CT scan of the abdomen or chest obtained while working up another problem. Other common presentations are non-resolving infiltrates after treatment for pneumonia, as a pleural effusion or with persistent chest wall or shoulder pain. Because of the endobronchial origin of many lung cancers, cough, hemoptysis, dyspnea, and unilateral wheezing or stridor may be the original complaint. Patients presenting with advanced disease may have weight loss, anorexia, fatigue, persistent fevers, or clubbing.

Lung cancers are associated with a number of syndromes, which can be divided into general categories: (1) the consequences of tumor invasion of the surrounding tissues, (2) the systematic effects of hormonal substances produced by cancers, and (3) cytokines or antibodies triggered by the immune system's response to the tumor (paraneoplastic syndromes). Local invasion of nerves at the apex of the lung causes Horner's syndrome (cervical sympathetic) or Pancoast syndrome (brachial plexus). Tumor invasion of the mediastinum can block venous return to the heart causing superior vena cava syndrome, invasion of the pericardium causing cardiac tamponade, or erosion into the esophagus causing obstruction or fistulas. Metastatic lesions in the spine can cause spinal cord compression with distal weakness and pain. Tumors can secrete antidiuretic hormone causing hyponatremia, parathyroid hormone causing hypercalcemia, or adrenocorticotrophic hormone leading to Cushing syndrome. These latter hormonal syndromes are more common with SCLC and reflect the neuroendocrine nature of these cancers. The most common paraneoplastic syndrome associated with lung cancer, occurring in 5–15% of patients, is periosteal swelling of the distal phalanges causing clubbing of the fingers. The myasthenia-like Lambert-Eaton syndrome develops from the production of antibodies to the postsynaptic acetylcholine receptor of the motor end plate.

Diagnostic Approach

Typically, patients with lung cancer present with advanced tumors causing a range of symptoms. Diagnostic decisions center on identifying the tumor cell type and accurately staging the extent of the cancer. With increasing frequency, especially in the context of screening for asymptomatic cancers using low-dose CT scans of the chest, diagnostic decisions revolve around the safest way to evaluate small, indeterminate lung nodules. Recent years have seen a rapid expansion in the complexity of diagnostic algorithms for both clinical scenarios. This complexity makes it beyond the scope of this chapter to make any detailed suggestions about workups for particular clinical presentations.

Evaluating a Lung Nodule

Lung nodules may be found incidentally on a chest X-ray or through a screening protocol using a CT scan. Incidental lung nodules should be compared with any prior imaging tests. An indeterminate nodule that can be shown to have been stable for at least 2 years requires no further diagnostic evaluation. Nodules found by chest X-ray that cannot be shown to be stable for 2 years should have a diagnostic, thin-section CT of the chest performed. Further evaluation is determined by the pretest probability of malignancy, the size of the nodule (greater than 8 mm or smaller), and nodule characteristics. Further diagnostic steps may include serial CT studies over 2 years, functional imaging with positron emission tomography (PET), bronchoscopy with biopsy, CT-guided needle biopsy, or surgical wedge resection. Based on the NELSON Trial, measuring nodule volume doubling time improves sensitivity and specificity for nodule characterization [22]. The choice of which technique to use should involve a team approach involving input from radiologists, pulmonologists, thoracic surgeons, and the patient's preferences. The family physician can play a crucial role explaining the risks and benefits of the various options to the patient and helping to make sure the final decision reflects the patient's values.

Staging Non-small Cell Lung Cancer

The diagnostic workup for a patient with a suspected lung cancer is based on the size and location of the

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suspected tumor, evidence for mediastinal or distant metastatic disease, the efficiency of the proposed workup, the invasiveness and risks of any procedures, the technologies and expertise locally available, and the patient's comorbidities and preferences. Diagnostic technologies are in a period of rapid evolution. It is reasonable to consult a team representing interventional radiology, thoracic surgery, pulmonology, and oncology. Accessing websites from groups such as the National Comprehensive Cancer Network or the American College of Chest Physicians can provide family physicians with current diagnostic guidelines. The family physician should conduct a thorough history and physical examination, including performance status and noting any weight loss. Routine studies should include the following: a CBC with platelets, a comprehensive metabolic profile, a CT scan of the chest and upper abdomen (including the adrenal glands), and a pulmonary function testing. Counseling on smoking cessation should be performed for current smokers. Discuss with the patient and participating consultants a plan for integrating palliative care into the treatment plan. When there is a high clinical suspicion for advanced disease, PET imaging allows for the choice of a diagnostic biopsy site to confirm the highest stage to be assigned to the cancer.

Staging Small Cell Lung Cancer

The diagnostic evaluation for suspected or known small cell lung cancer follows the same outline as for non-small cell lung cancer discussed above. The aim is to categorize the disease as in either a limited or extensive stage. In addition to the general workup reviewed above, a brain MRI is obtained. For equivocal bone lesions on PET imaging, bone imaging with MRI/radiographs as well as bone marrow aspiration/biopsy may be needed [23].

Treatment

Algorithms for treating lung cancer are now evolving rapidly after years of very modest progress. This has come about through an increased understanding of cancer genomics. Tumors harboring specific acquired genetic alterations are being treated with targeted inhibitors of altered enzymes that are driving cancer growth. Monoclonal antibodies targeted at altered epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and receptor tyrosine kinase (ROS1) are producing exciting clinical response rates [24–26]. The list of targeted mutations is growing rapidly [27]. An era of personalized treatment, based on whole tumor genome sequencing, is imminent. The family physician is in the position, working collaboratively with the consulting oncologist, to educate patients about these treatment options and to counsel them about the option of participating in an experimental treatment protocol. In addition, palliative care needs should be addressed throughout the treatment process.

Non-small Cell Carcinoma

Treatment algorithms are driven by stage, pathology, and mutation testing of the tumor. It is now possible to identify genetic mutations in lung cancer cells through circulating tumor DNA (ctDNA). This technology is beginning to replace invasive biopsies in some centers. This genetic focus on the tumor cell is shifting the treatment focus from cytotoxic chemotherapy to personalized choices of targeted monoclonal antibody based therapies [27]. Treatment decisions need to be worked out consensually between the patient and the treatment team of medical oncologists, radiation oncologists, and thoracic surgeons [28]. The family physician can help to facilitate these decisions and advocate for the patient's values and preferences.

Small Cell Carcinoma

The performance status of the patient with limited stage disease drives treatment decisions ranging from concurrent chemotherapy and radiation therapy for high-functioning patients to hospice care for patients with extensive

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comorbidities. Patients with extensive disease are treated with chemotherapy. Whole brain radiation therapy is used for patients with brain metastases. Palliative external beam radiation therapy can be used for bone metastases, superior vena cava syndrome, lobar obstruction, or spinal cord compression.

Posttreatment Follow-Up

With the earlier detection of lung cancers and more effective treatments, the family physician will be involved with a growing number of patients who have undergone therapy with curative intent who will need surveillance for recurrent disease. Coordinate this care with the treating oncologist. A history and physical examination, along with CT examinations of the lungs, should be done every 4–6 months for the first 2 years and then yearly thereafter. Encourage patients to remain current with influenza and pneumococcal vaccinations [29].

Palliative Care

The family physician can play a key role in ensuring as high a quality of life as possible for patients as they move through the continuum from diagnosis to treatment with intent to cure and finally to end-of-life care. The family physician can educate patients about creating a living will and a durable power of attorney to establish their care preferences. They can explore the patients' interest in the use of complementary and integrative therapies alongside standard cancer therapies. They should question patients about common symptoms such as pain, anorexia, constipation, breathlessness, fatigue, depression, and insomnia and provide care to ameliorate these as much as possible [30–32].

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Selected Disorders of the Respiratory System

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There are many respiratory disorders that will commonly be encountered by family physicians that are not addressed in other chapters of this text. This chapter briefly discusses the etiology, epidemiology, presentation, diagnostic criteria, and management of several selected disorders: pulmonary hypertension, pneumothorax, pleural effusion, interstitial lung disease, lung cancer, pulmonary sarcoidosis, and vaping-induced pulmonary injury.

Pulmonary Hypertension

The term pulmonary hypertension (PH) is used to describe a diverse group of disorders causing increased pulmonary arterial pressures; specifically, the mean resting pulmonary arterial pressure is greater than or equal to 25 mmHg. Symptoms may include fatigue and shortness of breath, although many patients are asymptomatic until later in the disease course [1]. The true prevalence of pulmonary hypertension is not clear with estimates ranging from 5 to 52 cases per million people [2]. Pulmonary hypertension can be broadly divided into five groups based on presentation, pathophysiology, and potential treatments [3]. The five groups can then be further subdivided based on the exact etiology of the patient's symptoms. Group 1, or pulmonary arterial hypertension, is associated with drug toxicity, connective tissue disorders, and congenital disease etiologies. Group 2 is due to left heart disease. Group 3 is due to lung disease or hypoxia. Group 4 is due to chronic thromboembolic disease or other pulmonary obstructions. Group 5 is due to unclear or multifactorial mechanisms [Table 1].

Diagnosis

The diagnosis of pulmonary hypertension is difficult as the symptoms tend to be vague and non-specific. Common presenting symptoms include fatigue, dyspnea on exertion, cough, and syncope [4]. Comorbid conditions such as COPD, obstructive sleep apnea, heart failure, and history of chronic thromboembolic disease should raise the index of suspicion, especially if symptoms were previously well controlled and have now worsened. Physical exam findings cannot be used to rule out pulmonary hypertension; however, elevated jugular venous pressure, peripheral edema, and parasternal heave may suggest severe disease [5].

Lab evaluation is not indicated as no specific findings exist. Ancillary testing with electrocardiogram (ECG) and chest X-ray (CXR) may be performed. CXR may reveal right-sided heart enlargement and/or dilation of the pulmonary arteries. ECG may reveal right heart strain, right axis deviation, and right atrial enlargement. Of note, a normal CXR or ECG does not exclude pulmonary hypertension. Pulmonary function testing may aid in the diagnosis of pulmonary hypertension by ruling in underlying conditions including COPD or pulmonary fibrosis. Patients may frequently have decreased diffusion capacity [3].

The most important non-invasive test in diagnosis of pulmonary hypertension is transthoracic echocardiography (TTE). TTE will assess peak tricuspid regurgitation in order to estimate pulmonary artery pressure and assign patients to low-, intermediate-, and high-risk groups. Right heart catheterization remains the gold standard to confirm the diagnosis of pulmonary hypertension [3].

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Table 1 Adapted from ECS/ERS guidelines comprehensive clinical classification of pulmonary hypertension [3]

Group 1: pulmonary arterial hypertension	Group 2: left heart disease	Group 3: chronic Lung Disease	Group 4: pulmonary artery obstruction	Group 5: multifactorial/ unclear
Idiopathic Hereditary Schistosomiasis infection Drugs: appetite suppressants, rapeseed oil, benfluorex Connective tissue disorders: systemic sclerosis, Raynaud's disease, SLE, mixed connective tissue disease Congenital heart disease	HFpEF HFrEF Valvular Disease Restrictive cardiomyopathy Constrictive pericarditis Pulmonary vein stenosis	Obstructive sleep apnea COPD Interstitial lung disease Restrictive lung disease Pneumoconiosis	Chronic thromboembolic Malignancy Benign tumors Parasites	Hemolytic anemia Sickle cell disease Thalassemias Gaucher's disease Glycogen storage diseases Sarcoidosis Chronic kidney disease

Based on current recommendations, several populations are at increased risk of developing pulmonary hypertension and therefore should be screened. Individuals with HIV should be screened if they possess an additional risk factor: female sex, hepatitis C positive status, or African American. Additionally, patients with hereditary hemorrhagic telangiectasias, congenital heart disease, and familial pulmonary arterial hypertension be screened as well [4].

Management

The most important aspect of primary care management of PH is early recognition and referral to pulmonary hypertension specialists for definitive management. Family physicians play an important part in the treatment of pulmonary hypertension and should help facilitate treatment once the underlying cause has been identified. There are also disease-specific considerations and monitoring guidance that primary care physicians should keep in mind for patients with pulmonary hypertension. All patients with pulmonary hypertension should receive age- and comorbidity-appropriate vaccinations.

Most published data on treatment of PH is specific to group 1 patients. Every 3–6 months these patients should be seen and undergo ECG to monitor for arrhythmias, dyspnea monitoring, and labs including CBC, BMP, and pro-BNP [3]. Every 6–12 months additional lab evaluation including TSH, troponin, iron studies, and blood gas analysis should be considered. Iron deficiency frequently exists in these patients and should be treated accordingly. Repeat echocardiogram and right heart catheterization occur every 6–12 months for disease monitoring [3]. Group 1 patients should be encouraged to exercise within the limitations of their symptoms.

Given the increased risk of serious obstetric complications, pregnancy and birth control should be discussed in all female patients with PH. Contraceptive management strategies are controversial as some treatment modalities for PH may interfere with estrogen, and vasovagal reactions during IUD placement may be poorly tolerated [3]. Appropriate preventative health strategies such as vaccinations against influenza and pneumococcal pneumonia should be emphasized.

The goal for patients with group 2 and 3 is optimal management of their underlying medical condition. Patients in group 4 generally benefit from lifelong anticoagulation and oxygen when needed for hypoxemia. There is limited data regarding treatment of group 5 disease. Encouraging social support and end of life planning are important tasks for family physicians in all patients with PH regardless of which group they belong to [3].

Pneumothorax

Pneumothorax is defined as the presence of air in the pleural space. It takes one of the following abnormal circumstances to allow air accumulation

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in the pleural space: communication between the alveolar spaces and pleura, communication between the atmosphere and pleural space, or gas-producing organisms in the pleural space. From a clinical standpoint, pneumothorax is classified as either spontaneous or nonspontaneous (iatrogenic or traumatic). Spontaneous pneumothorax is further subdivided as primary (without clinically apparent underlying pulmonary disease) and secondary (underlying pulmonary disease) [6].

Primary Spontaneous Pneumothorax

Primary spontaneous pneumothorax (PSP) has long thought to occur due to spontaneous rupture of a subpleural bleb (small thin-walled air pockets); however, recent evidence points to diffuse emphysema-like changes of the lung parenchyma as the more likely cause [7]. The classic patient with PSP is a tall, thin male. The most important risk factor is tobacco smoking, though cannabis smoking also has demonstrated strong association with bullous parenchymal disease [8]. PSP doesn't usually have a known trigger but may be preceded by precipitating factors including atmospheric pressure changes, exposure to loud music, and pollution. These precipitating factors explain why cases of PSP tend to exhibit a clustering effect. PSP has an incidence of 7.4–18 cases/100,000 in males and 1.2–6 cases/100,000 in females per year [6].

Diagnosis

Typically, patients present with an abrupt onset of ipsilateral chest pain with or without dyspnea. Pain may be localized over the site of pneumothorax or radiate to the ipsilateral shoulder. Symptoms can often be minimal and even totally absent (in stark contrast to the presentation of secondary spontaneous pneumothorax). Symptoms also tend to improve following presentation; worsening of symptoms is rare and suggests the development of complications such as hemopneumothorax [8].

Physical exam can be completely normal in small pneumothoraces [6]. Findings that may indicate pneumothorax include decreased or absent breath sounds, percussive hyperresonance, and reduced ipsilateral chest expansion. Significant hemodynamic compromise (tachycardia, tachypnea, hypoxia, etc.) is usually absent. Radiographic imaging confirms the diagnosis and allows estimation of pneumothorax size, with an upright posteroanterior chest radiograph being the modality of choice. Findings on X-ray include the displacement of the pleural line and absence of lung markings between the pleural edge and chest wall. Inspiratory images alone are sufficient for diagnosis. Occasionally the pneumothorax cannot be detected on simple radiographs, and a CT is required. Ultrasound can also be a very sensitive modality but is not routinely used to evaluate PSP [6, 8].

Management

Therapeutic options for PSP depend on the size of the pneumothorax and the severity of the patient's symptoms. Treatment focuses on evacuation of air, if necessary, and prevention of recurrence. As tension and hemodynamic compromise is rare in PSP, conservative initial management is an option. Assuming mild symptomatology and small size of the pneumothorax (less than 20% or less than 3 cm between the lung and chest wall), outpatient management with observation and close radiographic follow-up is a reasonable option [6]. If air evacuation is necessary, needle aspiration and chest drain insertion are both options; however, no consensus guidelines exist on recommended treatment. Recent evidence suggests that needle aspiration is effective for the initial management of PSP [7]. A large pneumothorax or significant symptoms increase the likelihood that simple aspiration will not be sufficient, thus requiring chest tube placement for definitive management [8].

Recurrence rates for PSP are approximately 33% irrespective of treatment modality. Recurrence prevention with pleurodesis

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procedure should be offered after a single episode of recurrence to those who are at professional risk (aviation personnel, divers) or if chest tube therapy fails to result in lung expansion [6, 8].

Secondary Spontaneous Pneumothorax

Secondary spontaneous pneumothorax (SSP) results as a complication of underlying lung disease. The most frequent associated underlying disorders are COPD with emphysema, cystic fibrosis, tuberculosis, lung cancer, and lung infections. Because these conditions already represent some level of lung compromise, SSP often presents as a more life-threatening event requiring intervention as opposed to PSP. Incidence is similar to that of PSP with a peak incidence between 60 and 65 years of age [6].

Diagnosis

As opposed to PSP, dyspnea is usually the most prominent clinical feature in SSP; other symptoms including chest pain, cyanosis, hypoxemia, hypercapnia, and acute respiratory failure can also be present and are generally much more severe. As with PSP, imaging with CXR and/or CT scan will confirm the diagnosis. Recurrence is much more common than in PSP; rates up to 80% are seen in conditions such as cystic fibrosis [6].

Management

Management of SSP targets air evacuation, symptomatic control, and prevention of recurrence. As the majority of patients with SSP have significantly decreased pulmonary reserve, most will require pleural drainage. No consensus exists on initial management, but most guidelines recommend immediate chest tube insertion. Given the increase risk of recurrence, prevention by pleurodesis procedure should be performed after the initial event [6].

Tension Pneumothorax

A tension pneumothorax constitutes a life-threatening emergency. It develops as a result of air moving through a pleural defect that acts as a one-way valve, opening during inspiration and closing during expiration, resulting in progressive pneumothorax volumes and further lung collapse. Eventually, shifting of the trachea and mediastinum away from the pneumothorax occurs leading possible cardiopulmonary compromise. Tension pneumothoraxes most often occur secondary to major chest wall trauma. Classically, patients with tension pneumothorax develop jugular venous distension and contralateral tracheal deviation; however, these are very late signs and much less commonly observed in real studies [9]. Acute respiratory distress is often the initial presentation, and cardiovascular collapse can rapidly occur without prompt intervention. Immediate needle decompression by insertion of a large bore needle into the pleural cavity at the midline of the second intercostal space releases the trapped air and results in improved cardiopulmonary status. Following needle decompression, placement of a chest tube and treatment of chest wall injuries are required [6, 9].

Family and Community Issues

Given the strong association between smoking and PSP in addition to its link to underlying respiratory disorders, smoking cessation interventions provide an excellent opportunity for family physicians to intervene at a population level to decrease risk factors for initial PSP, prevent recurrent pneumothoraces, and minimize the risk for underlying respiratory disorders that cause SSP.

Pleural Effusion

Pleural effusions are an accumulation of fluid in the pleural space as a result of disparity in the formation and resorption of pleural fluid. The presence and amount of pleural fluid is typically regulated by capillary oncotic pressure as well as

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capillary and interstitial hydrostatic pressure. Pleural effusions are very common in clinical practice, with an estimated prevalence of 400 cases/100,000. A plethora of disease processes can cause pleural effusions with the most common being congestive heart failure, hepatic cirrhosis, pulmonary infections, and malignancy [10].

Diagnosis

Patients with pleural effusions can present with a variety of symptoms including dyspnea, pleuritic chest pain, cough, and referred pain to the shoulder or abdomen. Some patients are asymptomatic. Due to the breadth of the differential diagnosis and the presenting complaints, a systematic evaluation must be undertaken to diagnose the underlying cause. Pulmonary exam may reveal decreased breath sounds, percussion dullness, or even a friction rub. Given the prevalence of congestive heart failure as a cause of pleural effusion, a careful cardiac exam can provide valuable insight. A chest radiograph is often the initial diagnostic study, while more sensitive CT is not usually necessary to diagnose a pulmonary effusion [11].

While history and physical examination can provide clues to the causes of pleural effusions, determination of the exact etiology can be very difficult. Thoracentesis and pleural fluid analysis (PFA) are the next steps in the evaluation process; PFA can lead to a definitive or presumptive diagnosis in approximately 95% of cases [10].

The initial step of PFA is determining if the effusion is transudative or exudative. The rationale for differentiating is that a transudative effusion can be effectively treated by addressing the underlying cause such as heart failure or hepatic cirrhosis. If the effusion is exudative, further investigation is required to identify the local pathology causing the effusion. Differentiating transudative from exudative effusions is best achieved by using Light's criteria. Table 2 outlines how pleural and serum protein and LDH are utilized in Light's criteria.

Gross appearance, cell count, and pH studies of the pleural fluid can also be of use. Limitations with Light's criteria do exist. Almost all exudative effusions will be correctly identified; however, in approximately 25% of cases transudates will be misclassified as exudates, usually in the case of diuretic usage in CHF patients. The majority of these errors occur in patients where exudative criteria are barely met and usually in only one of the three elements of Light's criteria [11]. If clinical suspicion exists that the effusion has been misclassified, additional calculations using serum-pleural fluid albumin gradient or serum-pleural fluid protein gradient can be helpful [12].

Transudative Effusions

Transudative effusions occur secondary to processes that increase the hydrostatic pressure or decrease the oncotic pressure in pulmonary capillaries. Additionally, an increase in negative pressure in the pleural space can also lead to these types of effusions. Congestive heart failure and cirrhosis are the two most common causes of transudative effusions [10]. Pleural effusions associated with CHF tend to be bilateral. In contrast, around 80% of effusions from cirrhosis with ascites are right sided. Less common causes of transudative effusions are nephrotic syndrome, urinothorax, peritoneal dialysis, and trapped lung [10].

Exudative Effusions

In contrast to transudates, exudates are caused by local processes that lead to increased capillary permeability causing leakage of serum contents. Malignancy and infections of the pleural space or lung parenchyma commonly produce exudative effusion. A plethora of less common etiologies also cause exudative effusion; these include chylothorax, pulmonary embolism, superior vena cava syndrome, aortic dissection, rheumatoid arthritis, systemic lupus erythematous, liver abscesses, and hepatitis [10].

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Table 2 Pleural fluid characteristics

Characteristics	Transudate	Exudate
Pleural fluid protein/serum protein ratio	<0.5	>0.5
Pleural fluid LDH/serum LDH ratio	<0.6	>0.6
Pleural fluid LDH	<2/3 the upper limit of normal serum LDH	>2/3 upper limit of normal serum LDH
pH	>7.40	<7.40
WBC count	<1000/uL	>1000/μL

Adapted from [11]

Management

Ultimately, treatment of pleural effusions targets controlling symptoms and treating the underlying disease process. With appropriate treatment, the majority of the pleural effusions will resolve or cause minimal symptoms. Some effusions may require long-term drainage with placement of a small caliber chest tube and outpatient drainage. In refractory pleural effusions, a pleurodesis procedure can be considered, but this practice is controversial [10].

Family and Community Issues

Given that pleural effusions commonly result from chronic disease processes, family physicians play an important role in their management. Our role ranges from coordinating chronic disease care interventions to formulating long-term goals to end of life discussions. These discussions and management decisions play a large role not only in the physical care and health of patients but also in their and their family's mental and psychological health.

Interstitial Lung Disease

Interstitial lung disease (ILD) is a term used to refer to a wide variety of pulmonary disorders that share similar clinical, radiological, or pathological criteria. Approximately 200 conditions cause interstitial lung disease; these include sarcoidosis, idiopathic pulmonary fibrosis, connective tissue disease manifestations, systemic lupus erythematous, radiation exposure, hypersensitivity pneumonitis, and non-specific fibrosis [13]. Unfortunately, only one in three cases of interstitial lung disease have an identifiable cause [13]. While the diseases that comprise interstitial lung disease are individually rare, together they affect more than 1.9 million people worldwide [14].

Diagnosis

Patients will often present with non-specific cardiopulmonary symptoms including dyspnea and cough. A detailed history will help the physician identify risk factors and previous exposures for one of the many causes of interstitial lung disease. Emphasis should be placed on obtaining smoking history, family history of pulmonary disease, a list of all medications regularly taken at any point in their lifetime, radiation exposure history, and occupational/hobby history. Establishing a patient's exercise tolerance will provide an assessment of the current disease severity [15].

Given the broad spectrum of possible causes and often non-specific initial presenting symptoms, the diagnosis of ILD often occurs through a multidisciplinary team utilizing clinical, radiologic, and pathologic data to establish the definitive diagnosis and severity. Physical examination is not reliable for establishing the diagnosis and may be normal. Crackles may be present on auscultation but may not present in granulomatous causes such as sarcoidosis. Clubbing of the fingers may be present and is a harbinger of severe

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disease if present [16]. Patients with suspected interstitial lung disease should undergo laboratory testing including urinalysis, complete blood count, complete metabolic panel, ANA, CPK, and aldolase as well as other laboratory testing suggested by the history that may help limit the differential [17]. Patients should receive a chest X-ray and high-resolution chest CT. Pulmonary function testing should also be obtained to help narrow the differential diagnosis [15].

Management

Management principles that apply to all types of interstitial lung disease include smoking cessation and referral to pulmonary rehabilitation. Specific therapy for each type of interstitial lung disease is reliant on an accurate diagnosis and may require referral to multidisciplinary specialist clinics [15].

Lung Cancer

Lung cancer is tied with breast cancer as the most common form of cancer worldwide and carries significant morbidity. In the United States, approximately 230,000 new cases and 142,000 deaths occur from lung cancer every year [18]. The incidence of lung cancer rose sharply in the early 1900s following the rise in cigarette smoking. After the surgeon general's report on the link between tobacco smoking and lung cancer in the 1960s, the incidence of lung cancer has progressively decreased. Besides cigarette smoking, other exposure risk factors including radon, arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, air pollution, second-hand smoke, and even fumes from cooking sources all increase the risk of lung cancer. Men, specifically African American men, are more commonly affected than women [19].

Subtypes

Lung cancer is commonly divided into two major types, small cell and non-small cell. Additionally, four histological subtypes exist: squamous cell, adenocarcinoma, large cell, and small cell. Non-small cell encompasses 80% of lung cancers. Small cell lung cancer (SCLC) possesses the worst prognosis due to its aggressive behavior and rapid doubling time [20]. Classically in SCLC, you will see massive lymphadenopathy and direct mediastinal invasion. SCLC also presents more commonly with paraneoplastic syndromes such as SIADH, ectopic ACTH production, and Lambert-Eaton syndrome [20].

Screening

The high incidence and significant morbidity associated with lung cancer necessitates appropriate screening. Annual low-dose chest CT without contrast is the most appropriate screening modality [21]. When compared to plain radiographs, low-dose CT screening demonstrated a 20% relative risk reduction in mortality. Current guidelines recommend annual low-dose CT in adults age 55–80 who possess a 30-pack year history and currently smoke or have quit within the past 15 years [21].

Diagnosis

Initial presentation of lung cancer can be varied. Most will present with some form of pulmonary complaint such as cough, dyspnea, chest pain, or hemoptysis. Many will also present with the classic symptoms of cancer such as unexplained weight loss and fatigue. Up to 25% of patients will be asymptomatic and only diagnosed because they underwent imaging for another reason. Pulmonary exam may reveal evidence of pleural effusion, wheezing, or pneumonia but most often is largely normal. Because symptoms can be so varied, the clinician must have a high suspicion in the right patient population and undertake appropriate evaluation [22].

The majority of decisions regarding advanced imaging, tissue diagnosis, and treatment options will not be guided by the family physician. Rather, an FP's role is to have an appropriate index of suspicion to initiate the work up in the appropriate

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patient. The first step in diagnosis is usually plain chest radiographs. Findings can range from a single pulmonary nodule to widespread disease with malignant pleural effusions. The three most important features of a pulmonary nodule that should raise the suspicion for malignancy are size (>20 mm), location in the upper lobes, or edges that are spiculated [20]. Several risk calculators exist that take into account pulmonary nodule characteristics as well as other patient characteristics (age, risk factors, etc.) to calculate malignancy risk of the nodule. Every patient in whom there is a suspicion for lung cancer should undergo a chest CT with IV contrast [20]. Family physician should coordinate further care and evaluation with the appropriate specialists.

Three basic questions need to be answered on patients with diagnosis of lung cancer: what the extent of the disease/metastasis is, what comorbidities exist that may limit treatment options (such as COPD), and are symptoms or evidence of paraneoplastic syndrome present that would require early treatment [20].

Once definitive diagnosis is made by tissue biopsy and treatment begins, the role of the family physician shifts to support and comfort. Assisting with treatment side effect management, addressing depression and other psychiatric comorbidities, and discussing end of life goals all fall within the purview of the patient's family physician.

Family and Community Issues

Given the significant morbidity of this disease as well as its association with smoking, the family physician's primary role needs to be one of primary and secondary prevention. Smoking cessation and appropriate screening are among the most effective things a family physician can do to combat this disease.

Pulmonary Sarcoidosis

Sarcoidosis is a multisystem, granulomatous disease of unclear etiology. Its effects can range from an acute self-limited process to progressive and debilitating multi-organ system dysfunction. Annual incidence is approximately 10 cases/100,000. African Americans are affected at four to ten times the rate of Caucasians; it is quite rare in those of Asian ancestry. Females are also affected at a higher rate than males. Peak age of presentation for men is between 40 and 59 and for women between 50 and 69. Despite extensive research, the etiology and pathogenesis of sarcoidosis is poorly understood. While classically affecting the lungs and intrathoracic lymphatic system, sarcoidosis commonly demonstrates extra-thoracic manifestations [23].

Diagnosis

Given the variety of organ systems that can be affected and lack of definitive diagnostic test for sarcoidosis, clinical suspicion with a thorough evaluation is necessary. As the lung is involved in greater than 90% of cases, patients will often present with pulmonary symptoms such as cough, dyspnea, or chest pain. Additional, non-specific symptoms include fatigue, malaise, fever, and weight loss. Dermatologic, hepatic, and ocular signs and symptoms may also be present [24]. Many cases are asymptomatic and are only incidentally found on radiograph. Physical exam often is normal unless the disease course is aggressive or advanced [24].

The diagnosis of sarcoidosis requires three essential elements: typical clinical and radiographic manifestations, exclusion of other disease processes, and proven histopathologic detection of noncaseating granulomas. Laboratory evaluation consists of complete blood count with differential, complete metabolic panel, urinalysis, HIV testing, and TB testing. Inflammatory markers such as ESR and CRP are non-specific but are often obtained. Classically, serum ACE levels are elevated in 75% of cases of sarcoidosis; however current testing modalities lack both sufficient sensitivity and specificity [25].

Radiographic evaluation plays a very important role in the diagnosis of sarcoidosis. Plain films commonly reveal bilateral hilar adenopathy but can also demonstrate parenchymal infiltrates

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and/or evidence of fibrosis. High-resolution CT scan of the lungs is often completed as well. PFTs can be useful in assessing respiratory impairment as well as monitoring disease improvement or progression [25].

Definitive diagnosis requires histopathologic findings of noncaseating granulomas. Transbronchial lung biopsy is often the modality of choice to obtain histology specimens. After confirmation of disease presence on pathology, a thorough evaluation for extrapulmonary involvement should be completed including electrocardiogram, echocardiography, and detailed fundoscopic evaluation. Regular visits should occur as almost a quarter of patients develop new system involvement within the first 2 years following initial diagnosis [25].

Management

Management decisions are based on expected prognosis, extent of disease/severity, and the patient's preferences. As many cases of sarcoidosis resolve spontaneously or are asymptomatic, therapy may or may not be necessary [26]. Sarcoidosis progression can be divided into three broad categories: acute disease which resolves within 2–5 years, chronic disease which persists beyond 5 years, and refractory disease which is chronic and progressive. Traditionally, first-line treatment consisted of corticosteroids; in recent years steroid-sparing therapies have gained popularity [26]. Steroids possess the advantages of being available, reliable, effective, and easily titrated; however, the plethora of known side effects and toxicities associated with long-term steroid use makes case by case decision-making imperative. Patients who possess comorbidities such as diabetes, osteoporosis, or psychiatric disorders may benefit from steroid-sparing therapies [27].

In the appropriate patient, treatment guidelines suggest initiating therapy with 10–40 mg of prednisone daily and regular titration until therapeutic response is obtained. This response is usually evident in 3–4 weeks. When adequate response is obtained, the dose can be slowly tapered every 3–4 weeks until the lowest required maintenance dose is determined; a goal of 10 mg of prednisone or less is reasonable [26]. Maintenance therapy usually lasts for at least 6 months. Relapse rates range widely between 14% and 74% with acute disease, usually occurring within the first 6 months of therapy discontinuation [26]. Relapses can occur up to 2 years after discontinuation. Initiation of the previously effective steroid doses usually regains control over symptoms. For patients with predominantly lung symptoms (cough, dyspnea), switching to an inhaled corticosteroid after a 3-month trial with systemic steroids has demonstrated improvement in symptoms [26].

Steroid-sparing treatment options such as methotrexate, azathioprine, leflunomide, and mycophenolate mofetil should be considered in chronic/refractory disease or in patients with high risk of steroid-related complications [25, 26]. Limited data exist comparing the effectiveness between these steroid-sparing therapies. Choice of treatment depends on clinician familiarity, patient preferences, and the presence of comorbidities. Currently, methotrexate is the most well studied. If there is disease progression or toxic effects, escalation of therapy with infliximab or adalimumab may be necessary [27] (Fig. 1).

Family/Community Problems

Often patients with sarcoidosis are being managed by specialists, particularly if they have chronic or refractive disease. The family physicians hold a unique role in the initial evaluation and more importantly monitoring appropriate healthcare maintenance issues for those on long-term steroids such as appropriate vaccinations, *Pneumocystis* pneumonia prophylaxis if needed, osteoporosis evaluation/management, etc.

Vaping-Induced Pulmonary Injury

E-cigarette or vaping product use-associated lung injury (EVALI) is characterized by pulmonary injury linked to the use of e-cigarette products.

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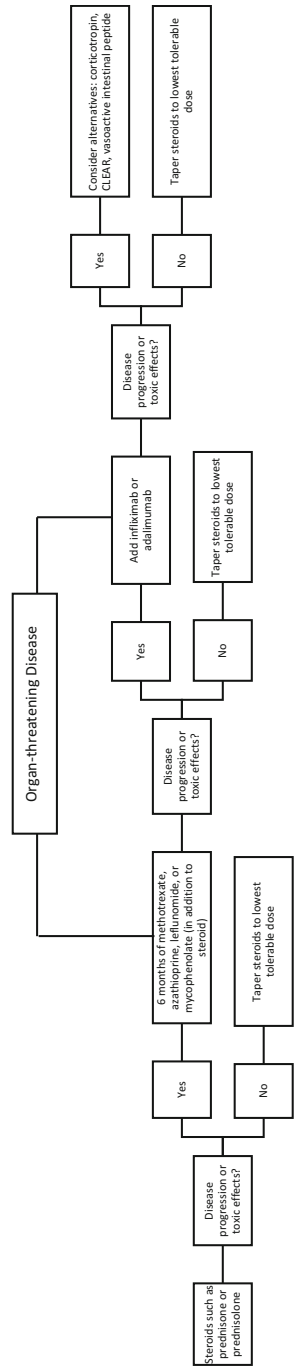


Fig. 1 Treatment strategies for patients with pulmonary sarcoidosis. (Adapted from [27])

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The initial outbreak of EVALI was identified in July 2019; since then over 2500 hospitalized cases have been reported. Patients commonly present with symptoms including cough, shortness of breath, and chest pain. Unfortunately, progression to acute respiratory failure is common [28].

While information about the exact etiology of EVALI is limited, one case series compared bronchoalveolar lavage specimens from patients with EVALI to healthy participants and found vitamin E acetate was found in the EVALI specimens. This suggests that vitamin E acetate-containing products may be related to the development of EVALI [29].

Diagnosis

Given the recent identification of the disease process, there is not yet an agreed-upon diagnostic criteria. For the purpose of clinical surveillance, the following diagnostic criteria have been proposed. Probable cases have been defined by a patient use of an e-cigarette 90 days prior to symptom onset, presence of pulmonary infiltrates on imaging, respiratory infection not believed to be the cause of the patient's symptoms, and no existing alternative plausible diagnosis. Confirmed cases were defined with the same criteria as probable except that pulmonary infection had been definitively ruled out with various infectious disease testing modalities [30].

Management

Management of EVALI is based on observational studies. Supportive care is the mainstay of treatment. In one case series, 95% of patients who presented with EVALI symptoms required hospitalization. Respiratory support is crucial to management with 53% of patients requiring ICU care and 26% requiring intubation. Many patients received glucocorticoids at the time of hospitalization and clinical teams reported improvement in their symptoms with steroid treatments [28].

Prognosis

Long-term prognosis data for EVALI are lacking. Of the 2409 cases reported to the US Center for Disease Control (CDC) since the summer of 2019, there were 52 deaths, 31 rehospitalizations (median 4 days after discharge), and 7 deaths after discharge (median 3 days after discharge). E-cigarette avoidance is the most important aspect of post hospital care [31].

Primary care physicians should regularly screen for e-cigarette and engage in targeted cessation counseling. The US Food and Drug Administration is currently engaged in efforts to reduce e-cigarette use in children by removing flavored e-cigarette products from the market. The CDC currently recommends against e-cigarettes [30].

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Part XIX

The Digestive System

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Gastritis, Esophagitis, and Peptic Ulcer Disease

91

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Dyspepsia/Epigastric Pain

Gastritis, esophagitis, and peptic ulcer disease (PUD) present commonly with epigastric pain or dyspepsia. Dyspepsia is defined as "a predominant epigastric pain lasting at least 1 month" and "can be associated with any other upper gastrointestinal symptoms such as epigastric fullness, nausea, vomiting, or heartburn, provided epigastric pain is the patient's primary concern." [1]. The

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recent Rome IV criteria for functional dyspepsia is the presence of at least one of the following: postprandial fullness, early satiety, epigastric pain or epigastric burning [2]. Dyspepsia is a common problem. Most patients have no organic cause and are defined as having functional dyspepsia.

Epidemiology

Dyspepsia is a common problem, with an annual incidence of 1–2% in the general population and a prevalence that may reach 20–40%. The four major causes of dyspepsia are functional dyspepsia (FD), PUD, gastroesophageal reflux disease (GERD), and gastritis. FD accounts for 70% of all causes of dyspepsia. Less common causes of dyspepsia are symptomatic cholelithiasis, irritable bowel disease, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina. Rarely, patients with coronary artery disease present with dyspepsia. Patients who seek medical attention for dyspepsia are more likely to be concerned about the seriousness of the symptom, worried about cancer or heart disease, and experiencing more stress than individuals who do not seek medical attention for dyspepsia.

Presentation

No single symptom is helpful for distinguishing between the different causes of dyspepsia, but some patient characteristics are suggestive of serious disease. For example, as single symptoms, nocturnal pain, relief of pain by antacids, worsening of pain by food, anorexia, nausea, and food intolerance are not helpful for determining the cause of dyspepsia. Patients older than 50–60 years or with alarm "red flag" symptoms (i.e., weight loss, anemia, dysphagia, persistent vomiting, gastrointestinal bleeding, hematemesis, and melena) are more likely to have a serious underlying disorder. With the possible exceptions of PUD and duodenitis, there is no clinically meaningful association between endoscopic findings and dyspeptic symptoms. It is important to inquire about the use of nonsteroidal anti-inflammatory drugs (NSAIDs), as their use is a frequent cause of PUD. Alcohol is a frequent cause of gastritis, esophagitis, and chronic liver disease/cirrhosis which may lead to portal hypertension and esophageal varices with risk of life-threatening gastrointestinal bleeding.

General Approach

Individuals with evidence of complications or alarm symptoms should be promptly evaluated with endoscopy and, as needed, hospitalized [1–3]. Because age is the strongest predictor of finding "organic" disease on endoscopy, individuals over the age of 50–60 years should also be evaluated with endoscopy. For the remaining patients, a test and treat strategy is recommended. Test for *Helicobacter pylori* by either urea breath test or stool antigen and if positive *Helicobacter pylori* eradication should by undertaken (see section on PUD). If negative, the patient should be treated with a proton-pump inhibitor (PPI).

If *Helicobacter* pylori negative, empiric treatment for functional dyspepsia consists of proton-pump inhibitors (PPIs), available over the counter or by prescription (Table 1). If a PPI fails to relieve symptoms, there are several options. Prokinetic agents such as metoclopramide may be tried. Tricyclic antidepressants are another option. If still without improvement, referral for psychotherapy should be considered [1, 3].

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a common problem with a prevalence of reflux of around 18% in North America, which can reach

Table 1 Usual daily dosage of antacid medications

Proton-pump inhibitors	
Omeprazole (Prilosec)	20–40 mg qd
Lansoprazole (Prevacid)	15–30 mg qd
Rabeprazole (Aciphex)	20 mg qd
Esomeprazole (Nexium)	20–40 mg qd
Pantoprazole (Protonix)	40 mg qd

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25–35% over a lifetime in the US population [4]. Around 5–10% of patients with GERD experience symptoms daily and nearly 44% on a monthly basis. The incidence of GERD increases during pregnancy, with obesity and tobacco use. GERD occurs when injurious gastric contents breech the esophageal-gastric (EG) junction with impaired luminal clearance but exact pathophysiology is unknown [5]. Exposure to excessive acid or pepsin can lead to damage of the esophageal mucosa, resulting in inflammation and ultimately scarring and stricture formation. Several factors may lead to GERD including hiatal hernia, incompetence of the lower esophageal sphincter (LES), inappropriate LES relaxation, impaired esophageal peristalsis and acid clearance, impaired gastric emptying, and repeated vomiting. Multiple prescription and over the counter medications lead to an increased risk of GERD. These include NSAIDS (most common), bisphosphonates, SSRI therapy, sirolimus, anti-platelets, chemotherapeutic agents, as well as certain anticholinergics, nitrates, narcotics, estrogens, diazepam, alpha-antagonists, theophylline, and beta-agonists. GERD may occur as an isolated entity or as part of a systemic disorder such as scleroderma. GERD is a risk factor for gastric ulcerations, esophageal strictures, Barrett's esophagitis, and esophageal adenocarcinoma, one of the fastest-growing cancers in the United States.

Presentation

The most reliable symptom of GERD is heartburn, a retrosternal burning sensation that may radiate from the epigastrium to the throat. Patients may also complain of pyrosis or water brash, the regurgitation of bitter-tasting material into the mouth. Belching is frequently described. Symptoms may be worse after eating, bending over, or lying down. Nocturnal symptoms may awaken the patient. GERD can cause respiratory problems including laryngitis, chronic cough, aspiration pneumonia, and wheezing. Atypical chest pain can also be caused by GERD. Finally, patients may complain of hoarseness, a globus sensation, odynophagia (pain with swallowing), or dysphagia. Red flag symptoms indicating a more serious etiology may include persistent nausea and vomiting, weight loss, bleeding, mass or iron deficiency anemia and would warrant further workup.

Diagnosis

A young patient with no evidence of systemic illness typically requires no further workup and can be treated empirically with a trial of PPI therapy and removal of insulting medications or lifestyle risks. This is both proven clinically and cost effective. Older patients greater than age 50 with new onset of symptoms, particularly those with above mentioned red flag symptoms, may warrant further evaluation. Upper endoscopy is the evaluation of choice [6]. Ambulatory 24-h pH monitoring is the most sensitive test for demonstrating reflux if endoscopy is negative although poorly tolerated by most patients. A barium swallow study or esophageal manometry may be necessary if a motility disorder is suspected, as endoscopy is often normal in patients with this problem and may point to a diagnosis of function dyspepsia.

Management

GERD is treated by both non-pharmacologic and pharmacologic means [6, 7]. Whereas patients with mild disease may respond to non-pharmacologic treatment, patients with moderate to severe symptoms or recurrent disease usually require medication therapy added or intensified, in addition to continuation of lifestyle changes.

All patients with GERD should be advised to reduce weight (if over their ideal body weight), avoid large meals (especially several hours before going to sleep), refrain from lying down after meals, and refrain from wearing tight clothing around the waist. Avoidance of certain food triggers such as alcohol, caffeine, chocolates, fatty and spicy foods, citrus fruits, and tomato-based foods can help with the symptoms. This treatment

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method has also demonstrated benefit in overall cardiovascular risk factors as well as the reduction of certain cancer risks. Patients who experience nocturnal symptoms often find relief by putting the head of the bed on blocks 4–6 inches in height. Sleeping on more pillows or on a wedge may be less effective because of nocturnal movements. Because nicotine lowers LES pressure, smoking cessation is recommended [8].

Patients who do not respond to lifestyle changes alone are treated with pharmacologic agents. H2 Receptor Antagonist (H_2RA) suppress acid secretion by competing with histamine, thereby blocking its effect on parietal cells of the stomach. H_2RAs are effective, but both daytime and nocturnal acid production may be necessary to sufficiently inhibited acid production. PPIs irreversibly block the final step in parietal cell acid secretion and are the most potent antisecretory agents available. The pharmacologic treatment of GERD can be approached in a stepwise process. For mild, intermittent symptoms, antacids or over the counter H_2RAs can be used, in twice daily divided dosing. For persistent or severe symptoms, PPIs are the mainstay of treatment. Studies done with omeprazole 40 mg daily have been proven effective and there has not been found to be a difference in different brand PPIs with respect to therapeutic efficacy [9]. PPIs are less effective when taken on an as-needed basis. They are effective when dosed daily before breakfast, although some patients may require twice daily (before meals) dosing to achieve symptom control and/or esophageal healing. Once a patient's symptoms are controlled, a trial of decreasing the dose of medication (e.g., from twice daily to once daily).

PPI do come with risk. This includes multiple drug interactions such as Plavix. They cause risk for fracture due to decreased bone mineralization; this was not observed with H_2RA [10]. Other long-term risks have included community-acquired pneumonia, dementia, and nutrient deficiencies [11]. For those patients with GERD who require maintenance medication, periodic examination coupled with efforts to try to reduce medication is warranted. Clinicians should avoid inappropriate prescribing of PPIs and other medications in the treatment of GERD and seek to decrease and "de-prescribe" medications where appropriate and tolerated. Patients often reach for over the counter antacids as initial treatment with possible long-term side effects which, at high doses, can cause constipation, diarrhea, osteomalacia (rare), milk-alkali syndrome, and rebound symptoms.

A concern in patients with chronic GERD is Barrett's esophagus. Barrett's esophagus is metaplasia of the cells of the distal esophagus and is considered a precancerous lesion. The risk of development of adenocarcinoma of the esophagus following a diagnosis of Barrett's esophagus may be as high as 2%. Unfortunately, neither aggressive medical therapy nor surgical therapy for GERD has been shown to alter the progression between Barrett's esophagus and esophageal adenocarcinoma. There is uncertainty as to the efficacy and optimal frequency of endoscopic surveillance of patients with Barrett's esophagus. When dysplasia, the stage between metaplasia and adenocarcinoma, is identified, the recommended frequency of surveillance with esophagogastroduodenoscopy (EGD) and repeat biopsy varies, depending on the severity of dysplasia.

For severe or refractory GERD, the initial approach should be to ensure that the patient is on maximal PPI therapy. If symptoms continue, the addition of a prokinetic agent such as metoclopramide should be considered. Metoclopramide can increase esophageal contraction amplitude, increase LES pressure, and accelerate gastric emptying, three of the most significant motility problems in the pathogenesis of GERD. Metoclopramide is a dopamine antagonist that can cause extrapyramidal symptoms and, rarely, tardive dyskinesia. This may limit its use.

Individuals who are intolerant or unresponsive to optimal medical therapy or non-adherent to medical therapy are suitable operative candidates. Laparoscopic fundoplication surgery has been shown to be effective, at least in the short term [12]. Bariatric surgery for obesity may also be helpful [6].

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Peptic Ulcer Disease

Peptic ulcer disease is defined by EGD as a break in the gastric or duodenal mucosal of greater than 5 mm. Those mucosal breaks noted to be less than 5 mm are defined by the term erosion. Peptic ulcer disease carries a 5–10% overall prevalence with as high as approximately 8.4% in the US population. This has led to PPI drugs being 2 of the top 5 medications sold in the United States. Most peptic ulcers are caused by either *H. pylori* or NSAIDs. Although infection with *H. pylori* appears to be common, most individuals with *H. pylori* do not develop ulcers. Peptic ulcers may involve any portion of the UGI tract, but ulcers are most often found in the stomach and duodenum. Duodenal ulcers are approximately three times as common as gastric ulcers and nearly 95% of patients with a duodenal ulcer are colonized with *H. pylori*. In the past, PUD was marked by periods of healing and recurrence. Successful treatment of ulcers associated with *H. pylori* infection greatly diminishes recurrences and may also decrease the risk of gastric ulcerations leading to gastric cancers, such as gastric adenoma as well as mucosal associated lymphoid tissue (MALT).

Presentation

Epigastric pain is the most common presenting symptom of both duodenal and gastric ulcer disease. The pain may be described as gnawing, burning, boring, aching, or severe hunger pains. Patients with duodenal ulcers typically experience pain within a few hours after meals and complete or partial relief of pain with ingestion of food or antacids. Pain related to gastric ulcers is more variable and may be characterized by pain that worsens with eating. Both duodenal and gastric ulcers may occur and recur in the absence of pain. Pain is variable among patients with both kinds of ulceration and correlates poorly with ulcer healing as documented by endoscopy. Older individuals often present with less pain and may present acutely in nearly 50% of patients with a three times higher mortality rate. Children often present with less localized symptoms but have a much lower rate of perforation or penetration. Physical examination may reveal epigastric tenderness midway between the xiphoid process and umbilicus, but maximal tenderness may sometimes be to the right of the abdominal midline. Abdominal rigidity is a "red flag" sign that can be associated with ulcer perforation and is an indication for prompt hospitalization and urgent surgical consultation. For other red flag symptoms, see the section on "Dyspepsia." Patients at higher risk include those patients with an BMI >25, tobacco, cocaine or alcohol uses, those on high-risk medications, an underlying hypersecretory disease state such as Zollinger-Ellison syndrome, systemic mastocytosis, vasculitis or carcinoid syndromes, CMV infections, or a history of radiation therapy. High-risk medications are similar to those which increase risks for GERD and esophagitis. NSAIDS are the most common of these medications and aspirin use is also a common trigger. Both of these medications should be discontinued as initial management, if appropriate. In those patients where this is not possible, they should be used in conjunction a PPI or transitioning to a COX-2 inhibitor. PPI do appear to reduce the risk of recurrent ulcers and time to next ulcer in patients on long-term aspirin therapy.

Diagnosis

There are two ways that PUD may be diagnosed. Unless the patient has red flag symptoms, a test and treat strategy for H. pylori is recommended as outlined in the "General Approach" section for "Dyspepsia" [13]. The use of proton-pump inhibitors, bismuth preparations, and antibiotics can suppress *H. pylori* and lead to false-negative results and should be discontinued at least 2 weeks prior to testing using urea breath testing. This is not required for stool antigen testing. Stool antigen testing is the less expensive of two options. An ulcer may also be diagnosed by either radiographic studies or endoscopy. Although duodenal and gastric ulcers can be diagnosed by UGI studies, upper endoscopy is the investigation of first choice. Gastric ulcers more than 3 cm in

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diameter or without radiating mucosal folds are more likely to be malignant. In addition to the indications listed earlier in the chapter, endoscopy should be considered in patients with persistent and refractory symptoms even in the presence of negative radiographic studies, those with a history of deformed duodenal bulbs (thus making radiographic examination difficult), and in patients with suspected or confirmed upper GI bleeding. If an ulcer is diagnosed endoscopically, a rapid *Campylobacter*-like organism urease test (CLO test) is a quick, sensitive test for determining the presence of *H. pylori.* False positives are uncommon while false negatives occur in approximately 5–10% of cases. The presence of *H. pylori* can also be determined histologically and by culture following biopsy at the time of endoscopy.

Most patients, especially those who are asymptomatic posttreatment, do not require documentation of eradication of *H. pylori.* If one wishes to test for cure, a urea breath test (4 weeks after therapy) or stool antigen test can be performed. Test of cure has been found to be neither cost effective nor practical.

Treatment

All patients with PUD who smoke should be advised to stop smoking as continued smoking can delay the rate of ulcer healing. Higher risk of ulcerations occurs with NSAID use due to submucosal erosions and inhibition of prostaglandins and COX-2 pathways, which stimulates bicarb production and mucosal blood flow. Whether or not a patient's PUD is associated with the use of an NSAID, existing NSAIDs should be discontinued and future NSAID use should be avoided and traditional antiulcer therapy begun with a PPI. For patients who test positive for *H. pylori,* antibiotic treatment should be given. A number of drug regimens have been shown to be effective [13, 14]. A PPI is part of every antibiotic regimen. Patients with *H. pylori*-negative ulcers are treated with traditional antacid agents without antibiotics for 4–6 weeks. In areas with high clarithromycin and metronidazole resistance, amoxicillin can be utilized as an option.

Treatments for the eradication of *Helicobacter pylori* are for 10–14 days and include the following options:

- PPI plus clarithromycin 500 mg BID, and amoxicillin 1 g BID or metronidazole 500 mg BID (Do not use in areas where clarithromycin resistance >15%).
- PPI plus bismuth subsalicylate 525 mg QID, metronidazole 250 mg QID, tetracycline 500 mg QID.
- PPI plus levofloxacin 500 mg daily, amoxicillin 1 gm BID.

In all of the above treatments, the PPI typically recommended is Omeprazole 20 mg orally twice daily. The first two options are considered the primary treatments for eradication of *H. pylori*.

There are a number of problems with the current antibiotic regimens. First, patient adherence may be a problem because of cost, duration of therapy, and side effects. GI side effects can occur with metronidazole, amoxicillin, and clarithromycin. Probiotics may reduce side effects during *H. pylori* eradication therapy. There is no difference in outcome between a 10- and 14-day course of therapy. A second problem is the emergence of antibiotic resistance involving both metronidazole and clarithromycin, which favors the use of the triple-antibiotic regimen or the levofloxacin containing regimen.

For patients with PUD and no documented *H. pylori*, all PPIs effectively heal ulcers in equipotent doses (Table 1). About 75–90% of ulcers are healed after 4–6 weeks of therapy. The PPIs heal ulcers more quickly than H_2RAs, but healing rates at 6 weeks are not significantly improved over those with H_2RAs. PPIs should be considered first-line medication therapy.

Dietary therapy should be limited to the elimination of foods that exacerbate symptoms and the avoidance of alcohol and coffee (with or without caffeine) because alcohol and coffee increase gastric acid secretion.

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Refractory Ulcers and Maintenance Therapy

Most duodenal ulcers heal within 4–8 weeks of the start of pharmacologic therapy. Gastric ulcers heal more slowly than duodenal ulcers, but 90% are healed after 12 weeks. Higher doses of H_2RAs (e.g., ranitidine 600–1200 mg/day) or PPIs may be used in an effort to heal refractory ulcers with an extended treatment course of 6–8 weeks [15].

Individuals with persistent or recurrent symptoms after completing a full course of pharmacologic therapy should be reevaluated. Adherence with previous treatment recommendations, as well as smoking cessation and avoidance of NSAID use, should be reviewed [16]. If no overt cause of treatment failure is identified, endoscopy should be performed to document ulcer healing. Antibiotic drug resistance may be a factor in persistence of ulcers secondary to *H. pylori.* Gastric cancer should be excluded by biopsy if a gastric ulcer remains unhealed (see section on "Gastric Cancer" below). Zollinger-Ellison syndrome should also be considered in the case of refractory ulcers.

In patients successfully treated for *H. pylori* or who have discontinued the use of NSAIDs, maintenance treatment with H_2RAs or PPIs should not be needed. Patients with ulcers in the absence of *H. pylori*, complicated PUD (e.g., bleeding or perforation), a history of refractory ulceration, aged greater than 60 years, or a deformed duodenum are candidates for maintenance therapy with H_2RAs or PPIs.

Gastritis/Gastropathy

Gastritis represents a group of entities characterized by histologic evidence of inflammation. Gastropathy is characterized by the absence of histologic evidence of inflammation of the gastric mucosa. Both gastritis and gastropathy may be either acute or chronic. It may be difficult to distinguish the two entities by clinical, radiographic, and endoscopic examinations. Gastritis and gastropathy may occur simultaneously and/or overlap with conditions such as GERD or PUD or may be a manifestation of less common conditions such as Crohn's, celiac disease, or sarcoidosis.

Acute gastritis may be due to infections (mainly *H. pylori*; less commonly viral, fungal, mycobacterial, or parasitic etiologies) and autoimmune conditions (e.g., pernicious anemia, eosinophilic gastritis). Histologic variants of uncertain cause include lymphocytic and eosinophilic gastritis. Gastropathy is commonly due to medications (e.g., NSAIDs including aspirin and cyclooxygenase-2 (COX-2) inhibitors, bisphosphonates, potassium, and iron), alcohol, refluxed bile, ischemia ("stress," as is seen in patients with shock, sepsis, trauma, or burns), or vascular congestion (as in portal hypertension or congestive heart failure).

Chronic gastritis may be preceded by episodes of symptomatic acute gastritis (e.g., that due to *H. pylori*) or present without prior warning with dyspepsia and constitutional symptoms. *H. pylori* is the most common cause of chronic gastritis; this association may be accentuated in patients receiving chronic PPI therapy. Pernicious anemia may be associated with chronic gastritis.

These conditions range in presentation from asymptomatic to life-threatening. Of particular interest to the clinician are acute and chronic erosive changes that may be complicated by symptomatic anemia or frank hemorrhage (presenting with melena or hematemesis – see section "Upper Gastrointestinal Bleed" below) and chronic atrophic changes that may progress to gastric cancer. Treatment consists of managing the underlying disease and removing gastric irritants.

Upper Gastrointestinal Bleed

Upper gastrointestinal bleed is defined as GI blood loss above the ligament of Treitz [11]. If the bleeding is clinically evident, it may present in one of three ways. Hematemesis may be bright-red or coffee ground-appearing material and usually is indicative of active bleeding. Melena signifies that the blood has transited

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through the GI tract, digestion of the blood resulting in dark coloration and sticky texture and is also found in lower GI bleeding. And finally, although uncommon, a UGI bleed may present as hematochezia if bleeding is brisk. If subacute or chronic, the UGI bleed may be discovered during the workup of iron-deficiency anemia or hemoccult-positive stools.

Causes

The four most common causes of UGI bleeding are: peptic ulceration, gastritis/gastropathy, esophageal varices, and esophagogastric mucosal tear (Mallory-Weiss syndrome). The causes of gastritis/gastropathy are described above. Bleeding due to varices is usually abrupt and massive. Varices may be due to alcohol cirrhosis, portal vein thrombosis, or any other cause of cirrhosis/portal hypertension. This includes nonalcoholic steatohepatitis, or NASH/"fatty liver" – an increasingly common condition and frequently associated with obesity and the metabolic syndrome. Mallory-Weiss syndrome classically presents with retching followed by hematemesis. Other causes of UGI bleeding include gastric carcinoma, lymphoma, polyps, and diverticula.

Diagnosis and Management

The diagnosis and management of the patient with UGI bleeding depends on the site and extent of bleeding. Vomitus and stool should be tested to confirm the presence of blood. Initial management for all patients includes assessment of vital signs including orthostatic changes. Patients with significant blood loss should be hospitalized and typed and matched for blood replacement and large-bore intravenous lines placed for fluid and blood replacement.

Though a nasogastric tube can be placed to evaluate gastric aspirate for resolution of intragastric bleeding and clearance of clots and particulate, the routine placing of a nasogastric tube for diagnosis or therapeutic effect is not required [18, 19].

Once the patient is hemodynamically stable, upper endoscopy can be performed. Rapid upper endoscopy upon presentation of patients in stable condition may hasten diagnosis and limit hospitalization. Endoscopy may not reveal an obvious source of bleeding when bleeding has ceased. Massive hemorrhage from varices can make endoscopy impractical. The other more common causes of upper GI bleeding will be readily apparent with use of endoscopy. If the patient continues to bleed and a source has not been identified, angiography may be used to identify the source of bleeding. Upper endoscopy can be therapeutic as well as diagnostic; sclerotherapy or ligation of esophageal varices can be performed through the endoscope. A variety of endoscopic treatments are available for bleeding peptic ulcers.

When bleeding is refractory to medical and endoscopically administered therapies, transcatheter arterial embolization or surgery (resection or shunting) should be considered. Though only 2.5–5% of upper GI bleeding cases require operative intervention, early surgical consultation is advised.

There are two additional therapies for bleeding varices [20]. Peripherally administered vasopressin or somatostatin or balloon tamponade are effective alternative treatments for bleeding varices.

Prevention of GI bleeding is more effective than treatment. Smoking and alcohol cessation should be recommended and NSAIDs avoided. Treatment of *H. pylori*-positive PUD or maintenance therapy for *H. pylori*-negative PUD may decrease subsequent bleeding episodes. Nonselective beta-blockers (propranolol or nadolol) can be used to prevent a first-time episode of bleeding in patients with known varices who have never bled [21].

Gastric Cancer

The overall incidence of gastric cancer has declined significantly in the United States since the 1930s. There has been a shift in prominence from distal to proximal stomach cancers. Individuals moving from Japan to the United States lower their risk of gastric cancer, suggesting that dietary

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and environmental factors play roles in the pathogenesis of this disorder. Additional risk factors include *H. pylori* infection, gastric polyps, and chronic gastritis.

The majority of gastric cancers are adenocarcinomas. Early gastric cancers are usually asymptomatic. As the cancer grows, patients may complain of anorexia or early satiety, vague discomfort, or steady pain. Weight loss, nausea and vomiting, and dysphagia (more common with proximal cancers) may also be present. Rarely, paraneoplastic manifestations occur. The physical examination is usually normal in patients with early disease, but a palpable abdominal mass or supraclavicular nodes, enlarged liver, or ascites may be present with advanced or metastatic disease. Patients with gastric cancer may present with GI bleeding, overt or otherwise occult, although this represents a minority of presentations.

Upper endoscopy is the preferred test when gastric cancer is suspected. Upper gastrointestinal (UGI) X-ray studies can detect gastric cancer, but it is not as accurate, and biopsy of suspicious lesions can be obtained during upper endoscopy. If an ulcer is suspicious in appearance, alarming symptoms are present, or if the patient is >45 years of age, EGD with biopsy is the preferred procedure. If the initial biopsies are benign, then endoscopy should be repeated at 12 weeks to ensure that the ulcer has healed completely. Benign gastric ulcers should heal within 6–12 weeks.

Prognosis for gastric cancer is generally poor, with a 5-year overall survival rate of < 5% [22]. Surgical treatment is the only chance for definitive cure. Perioperative or postoperative adjuvant chemotherapy is considered standard of care. The addition of postoperative radiation therapy has not been shown to offer survival benefit [23].

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Diseases of the Small and Large Bowel 92

Corin Archuleta, Matthew Wright, Anne Marie Kennedy, and Sara DeSpain

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Infectious Diarrhea

There are approximately 179 million cases of acute diarrhea illness in the United States each year. Worldwide, gastroenteritis accounts for two to three million deaths per year, most frequently at the extremes of age in developing countries. Diarrhea is defined as the passage of three or more unformed stools per day or the passage of more than 250 g of unformed stool per day. Acute

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diarrhea lasts less than 14 days. Diarrhea that persists for more than 3 weeks is considered chronic. A general approach to these patients involves defining the diarrhea to include volume and blood or mucus content, assessing for risk factors, assessing for invasive disease, determining the level of dehydration, and performing testing when indicated [1, 2].

Viral Gastroenteritis

Viral pathogens are the most common cause of gastroenteritis in the United States. Presentation is sudden onset, with copious amount of diarrhea frequently associated with nausea and vomiting. The disease is a self-limited process. The incubation period averages 24–48 h and symptoms between 24 and 60 h. Before the advent of the rotavirus vaccine, this was the most prevalent. Now *Norovirus* and, to a lesser extent, *Calicivirus* and *Sapovirus* are the most common agents. Viral gastroenteritis (VGE) typically arises in one of three settings: sporadically in infants/young children, as outbreaks on cruise ships or military barracks and healthcare facilities, and occasionally sporadically in adults. *Norovirus* is highly contagious, with an inoculum of as few as ten viral particles needed to infect patients. Routine testing is not useful in VGE. Symptomatic treatment with Zofran from 4 to 8 mg every 4–6 h can be safely offered to most patients. Most will recover spontaneously without medical intervention, though for the young and old, close monitoring of hydration status to prevent more severe outcomes may be necessary [2, 3].

Bacterial Infections

Bacterial infections typically cause inflammatory diarrhea illness. The bacteria are invasive or produce toxins, which lead to a more severe diarrheal presentation. *Escherichia coli*, *Salmonella*, *Campylobacter jejuni*, *Yersinia*, and *Shigella* are the most relevant organisms implicated.

E. coli is acquired by ingestion of raw or undercooked meat/poultry or unpasteurized dairy products. The bacteria are divided into two types: Shiga toxin-producing and non-Shiga toxin-producing. Of the Shiga toxin-producing strains (STEC), *E. coli* O157:H7 is the most well-studied. Other strains of *E. coli* are enteropathogenic, enteroinvasive, and enteroaggregative. The enterotoxigenic strain is associated with traveler's diarrhea, discussed further below. Shiga toxin-producing strains present with abdominal pain, cramps, and severe, often bloody diarrhea. Renal failure is a possible severe complication. A stool test for the presence of Shiga toxin should be completed before treatment with antibiotics, as this could precipitate hemolytic uremic syndrome [4, 5].

Salmonella infection arises from ingestion of contaminated eggs or dairy products. *Salmonella* usually causes gastroenteritis but can also cause typhoid fever, localized infection in bones/joints/meninges, and an asymptomatic carrier state. Up to 75% of *Salmonella* gastroenteritis cases follow the typical course of a bacterial diarrhea illness, with the resolution of fever, diarrhea, and nausea/vomiting after 2–4 days. Infection is diagnosed by stool culture. Typical mild infections do not warrant treatment. In chronic carriers, a course of ciprofloxacin 750 mg twice a day for 4–6 weeks may be used for treatment [4].

Campylobacter jejuni is typically found in contaminated water, milk, or meat and poultry. Domestic pets can also be carriers of the bacteria. Typically, the clinical syndrome begins with 24 h of fever and malaise, followed by the usual gastrointestinal symptoms: abdominal pain, nausea, vomiting, and diarrhea. Guillain-Barre syndrome has been reported to develop within 2 months in 1–2 of 10,000 cases. A stool culture is required for diagnosis. Treatment should be initiated if the clinical course lasts longer than 7 days. Erythromycin is the agent of choice dosed at 500 mg twice daily for 5 days [5].

Yersinia produces a clinical syndrome that typically lasts longer (10–14 days) than the other bacterial pathogens. It may cause mesenteric adenitis that mimics acute appendicitis. Additionally, the bowel wall nodularity and mucosal thickening on imaging can appear similar to Crohn's colitis features. Critical illness is treated with TMP-SMX one to two tablets twice a day.

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Shigella can cause severe invasive diarrhea with blood and mucus production. Stool culture is necessary for diagnosis. Treatment is with ciprofloxacin 500 mg two times a day for 3 days.

Traveler's Diarrhea

Traveler's diarrhea is the most commonly identified post-travel diagnosis according to the global travel surveillance project by the GeoSentinel Surveillance System. The CDC states 30–70% of travelers are affected. In contrast to the most infectious diarrhea, TD is most often attributed to a bacterial agent. Globally, enterotoxigenic *Escherichia coli* (ETEC) is the most common, followed by *Campylobacter jejuni*, *Shigella* spp., and *Salmonella* spp. The counseling provided to the patient in a travel or family physician's clinic is crucial to the appropriate recognition and treatment of TD [6–8].

TD is defined as three or more stools with or without associated fevers, abdominal cramps, and vomiting within 24 h. The International Society of Travel Medicine adds a functional classification, which practitioners might find helpful in discussing TD with patients (Table 1).

Rates of TD have persisted despite the adage for prevention of "boil it, cook it, peel it, or forget it." Preventive measures for patients include proper food and beverage selection, handwashing recommendations, and prophylactic medications. Expressly, travelers should be advised to drink only sealed beverages with no ice, avoid consuming salads or uncooked vegetables, peel fruits themselves if possible, only consume pasteurized milk and milk products, and avoid undercooked meat. Additionally, poor hygiene practices in local restaurants pose a significant risk factor for the development of TD [1, 6, 7, 9].

Table 1 Adapted from *Journal of Travel Medicine* consensus statement

Mild	Tolerable and not distressing Does not interfere with planned activities
Moderate	Interferes with planned activities
Severe	Incapacitating Includes all dysentery
Persistent	Symptoms last longer than 14 days

A strategy that relies solely on risk avoidance is often at odds with patients' goals of travel being to immerse themselves in the destination local culture. Therefore, thorough counseling on region-specific risks, endemic viruses, recommended vaccines, and prophylactic medicine is of paramount importance. It is also crucial to counsel about recognition of dysentery, acute versus chronic diarrhea, and when to seek medical care.

Commercially available vaccines against *Salmonella enterica* (typhoid fever) and *Vibrio cholerae* (cholera) exist, but are not recommended, primarily due to a lack of efficacy. Options for prophylactic medications include bismuth subsalicylate (BSS) and antibiotics. BSS can bind to bacterial toxins and protects the gut mucosa. It is recommended because of the effectiveness in reducing the incidence of TD by up to 50% and its safety profile. Adverse effects are mild and include black discoloration of tongue and stools, tinnitus, and constipation. It should be avoided in those who are allergic to aspirin, have renal insufficiency, are pregnant, or are on anticoagulants. Studied effective doses of BSS are 2.1 g/day or 4.2 g/day in four divided doses (meals and bedtime) [7, 9].

It is recommended to avoid prophylactic antibiotics unless the patient is at high risk of complications if they develop TD or if the traveler has essential duties and jobs to perform. When indicated, rifaximin in doses of 200–1100 mg daily can be used. This poorly absorbed antibiotic has fewer adverse effects than the previously recommended fluoroquinolones. *Campylobacter* spp. are resistant to rifaximin, so if travel is to South or Southeast Asia, another prophylactic agent should be used. There is insufficient data to recommend probiotics in the prevention of TD [6].

Treatment of TD depends on severity of disease and includes the management of fluid and electrolyte status, antimotility agents, and antibiotics. In mild to moderate cases, when the patient can tolerate oral intake, oral rehydration solutions (ORS) are strongly recommended. Packets of

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World Health Organization ORS are widely available in the developing world and involve dissolving one salt packet in 1 liter of boiled or treated water. There is strong evidence for the use of BSS or the antimotility agent loperamide for symptom control. Loperamide has an FDA indication for use in TD and can reach therapeutic effect within 1 to 2 h of the first dose. Loperamide (starting dose of 4 mg) is taken at the onset of symptoms. With each additional stool, another 2 mg can be taken. Travelers should be cautioned about the time to effectiveness, as rebound constipation can develop. Do not use loperamide if fever, bloody diarrhea, or severe abdominal pain is present [1, 7, 9].

In severe cases, when the patient cannot maintain hydration status orally, intravenous fluids should be used. Antibiotics can reduce the duration of symptoms to about a day and a half. Treatment is ciprofloxacin 500–750 mg for 1–3 days. The FDA warning cautioning against use of fluoroquinolones (FQs) in patients with aortic aneurysms and the rare risk of tendon rupture is reduced by newer one-dose regimens. There is widespread *Campylobacter* spp. resistance to FQs in Southeast Asia. Azithromycin is an alternative treatment for moderate TD and should be the first-line agent for severe cases or dysentery. A single 1 gram dose of azithromycin has been proven effective but is better tolerated with divided 500 mg dosing [1, 9].

Thorough counseling, in a travel or primary care clinic, prepares travelers with avoidance and management strategies for TD. Upon return from travel, if the patient is experiencing persistent or refractory diarrhea, antibiotic-resistant bacteria, *Clostridium difficile*, or protozoal parasite infection should be suspected and tested for with a stool sample.

Clostridioides difficile Infection (CDI)

Clostridioides difficile is a gram-positive spore-producing anaerobic bacillus. Bacterial virulence is the result of cytotoxin (A and B) release, which causes colitis. Disruption of gut microbiome with the overgrowth of *C. difficile* results in severe watery diarrhea and significant morbidity and mortality. Transmission is by the fecal-oral route or from direct exposure to a contaminated environment. The spores formed are heat, acid, and antibiotic resistant and can survive outside the colon. Infection control and patient contact precautions are a crucial part of disease control [10].

The most well-established risk factor for CDI is antibiotic use, specifically clindamycin followed by cephalosporins and FQs. Other risk factors include age over 70, enteral feeding, inflammatory bowel disease, or chronic kidney disease. CDI is now the most commonly reported nosocomial pathogen in the United States and is associated with an estimated 4.8 billion dollars in healthcare costs [10, 11].

CDI should be suspected in patients who present with profuse watery diarrhea (particularly with mucus or small amounts of blood), mild abdominal pain or cramping, fever, or malaise especially with recent antibiotic use or hospitalization. The Infectious Diseases Society of America (IDSA) recommends reserving testing for patients with acute, unexplained diarrheal illness with >3 stools in 24 h. They additionally discourage testing on infants younger than 12 months, given the high rates of normal colonization in that demographic.

Diagnosis is established by stool testing for the *C. difficile* toxin or genes that encode them. Most labs will not accept formed stool samples for analysis. Available lab tests include enzyme immunoassays (EIAs) for toxins A and B or glutamate dehydrogenase (GDH) and nucleic acid amplification testing (NAAT) to detect genes that encode the toxins. Clinical suspicion should drive the decision of which test to order. If clinical suspicion is high, a NAAT can establish the diagnosis. In cases of low clinical suspicion, the high sensitivity of EIA testing for toxin and GDH make it a useful screening tool. Concordant results confirm the diagnosis of *C. difficile*. Incongruent results can be followed up with NAAT [10–12].

The following ancillary laboratory testing assists in qualifying severity of disease and patient disposition: complete blood count (CBC) for peripheral leukocytosis and lactate and complete metabolic panel (CMP) for hypoalbuminemia and

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Table 2 CDI classification

Non-severe	WBC count of <15,000 per mL Serum creatinine level <1.5 mg per dL
Severe	WBC count >15,000 per mL Serum creatinine level >1.5 mg per dL
Fulminant	Hypotension Shock Ileus Megacolon

renal injury. Diagnostic imaging augments laboratory findings of disease severity. Plain radiographs can show ileus or distention >10 cm. Computed tomography (CT) findings include wall thickening, signs of mucosal/submucosal edema, peri-colonic stranding, and ascites [12].

Treatment of CDI involves fluid and electrolyte management, stopping the offending antibiotic agent, initiating treatment antibiotics, and possibly surgical intervention. The classification of disease into non-severe, severe, and fulminant, as outlined in Table 2, can help guide treatment. Oral vancomycin and fidaxomicin, in fixed or pulse/taper dosing, are the mainstays of treatment. For initial non-severe or severe episodes, the preferred agent is vancomycin 125 mg orally four times a day for 10 days. Fidaxomicin 200 mg orally twice a day for 10 days is equally efficacious but cost prohibitive. The regimen for fulminant CDI is vancomycin 500 mg orally or via nasogastric tube four times a day plus metronidazole 500 mg IV every 8 h. Recurrence occurs in up to 25% of cases; for those with recurrent infection, a pulse/taper regimen is recommended. The proposed mechanism of pulsed dosing is the spores are allowed to germinate and enter a vegetative form, thus rendering them susceptible to the antibiotics [10, 11].

For patients with disease refractory to conventional treatment, fecal microbiota transplantation (FMT) can be considered. FMT is low cost, with high apparent safety and a cure rate of 90%. FMT utilizes stool from a healthy donor, prescreened for communicable diseases. After donor selection and collection, the distillate is transplanted into the donor via NG tube, oral capsules, enema, or colonoscope. FMT introduces healthy flora from the donor to grow and replace the disrupted flora of the affected patient [13].

Surgical consultation is indicated in severe CDI or CDI complicated by ileus or toxic megacolon and should be considered early. Delayed operative treatment >3 days after admission is associated with higher mortality rates [11].

Parasitic Infections

Parasitic infections have a high worldwide prevalence, with a significant morbidity and, occasionally, mortality burden. They are mainly associated with poor sanitation in poverty-stricken areas. The signs and symptoms of parasitic infections include abdominal pain, diarrhea, and potentially weight loss. Parasitic infections can be further divided into two categories: protozoa and helminths. Protozoa are single-celled organisms that multiply in their hosts and include *Giardia*, *Cryptosporidium*, and *Entamoeba histolytica*. The helminths are a group of roundworms and flatworms with more complex life cycles.

Protozoa

Giardia intestinalis is the most common intestinal parasite in the United States. Outbreaks occur from ingesting contaminated water. *Giardia* cysts are ingested and, in the neutral environment of the small bowel, transform into its trophozoite form, enabling replication. Symptoms of infection include diarrhea, flatulence, and steatorrhea. Diagnosis is made by the presence of cysts in stool culture or antigen testing using enzyme-linked immunoassays. Treatment is metronidazole 500 mg orally three times a day for 5 days [14, 15].

Cryptosporidium is spread via contaminated water or from person-to-person. The protozoan can complete its entire life cycle in one human host's small intestine epithelia. This intestinal parasite has a self-limited course in immunocompetent hosts. It is characterized by 2 weeks of voluminous watery or mucus-containing diarrhea occasionally with nausea, vomiting, abdominal pain, and fever. In immunocompromised patients, especially those with acquired immunodeficiency syndrome (AIDS), the most common presentation is chronic diarrhea, lasting months or more. Most

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patients with AIDS never clear the infection, resulting in profound weight loss and extra-intestinal manifestations (biliary cryptosporidiosis). Diagnosis is confirmed by oocyst detection on microscopic examination of the stool with acid-fast staining. There are no effective treatments [14–16].

Amoebiasis caused by *Entamoeba histolytica* is a severe form of protozoal infection. The organism is ingested in feces-contaminated food and water and is endemic to Mexico, Central and South America, Asia, and Africa. Sexual transmission is possible, particularly in men who have sex with men. Virulent strains produce the proteinase histolysain and facilitate an invasion of the bowel wall and sometimes liver abscess formation. Treatment is with metronidazole and diloxanide for 10 days [17, 18].

Helminths

Helminths are further divided into three categories: cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes). As with protozoal infections, these are mostly associated with contaminated water supplies, undercooked meats, and poor sanitation and are endemic in developing countries.

Cestodes, or tapeworms, have a complex life cycle that starts with the ingestion of eggs by an intermediate (often animal) host. Consumption of undercooked meat from an infected animal leads to human infection. Thoroughly cooking the meat before consumption will kill any cysticerci. The parasite develops into its adult form in the definitive host's small intestine, completing its life cycle. The cestodes of clinical significance in humans are *Taenia saginata* (beef tapeworm) and *Taenia solium* (pork tapeworm). Symptoms of *T. saginata* are usually mild and might only be noticed by passing segments of the cestode in the stool. Conversely, *T. solium* eggs can implant in various tissues, including the brain, causing serious harm. This condition, known as neurocysticercosis, causes seizures and results in 50,000 deaths annually worldwide. Treatment is with albendazole or praziquantel [14, 15, 19].

Nematodes include *Ascaris lumbricoides*, *Necator americanus*, or *Ancylostoma duodenale* (hookworms), *Strongyloides stercoralis*, and *Enterobius vermicularis* (pinworms). There are multiple routes of infection, including fecal-oral, direct contact with infected soil or water, and ingestion of infected meat. The nematode life cycle requires a human host to ingest an egg. It then invades the vasculature of the small intestine and migrates to the lungs. Larvae develop in the alveolar spaces, ascend the airway, and are subsequently swallowed. The larvae mature in the small intestine and lay eggs into the bowel lumen, which are then expelled in feces [19].

Enterobius vermicularis, or pinworms, is the most common helminth infection and is equally prevalent among all socioeconomic levels. After defecation, gravid females migrate to the perianal and perineal regions to deposit their eggs. The eggs cause a pruritus, relieved by itching, but resulting in egg transfer underneath fingernails and subsequent reingestion. Infection can also be sexually transmitted. The most common presentation is perianal and perineal pruritus with restless sleep. Diagnosis is made clinically, with the "tape test." An adhesive is applied to the perianal region early in the morning and examined for eggs. A single dose of albendazole 400 mg is sufficient treatment, but given the high occurrence of reinfection, a second dose should be given 2 weeks later.

Ascaris lumbricoides infects up to a fourth of the world's population and causes 20,000 deaths a year. Most infections are initially asymptomatic, but after approximately 3 months, the worm burden is high enough to produce symptoms: abdominal discomfort, dyspepsia, loss of appetite, or nausea. A large worm burden can cause small bowel obstruction or rarely invade the hepatobiliary system causing biliary colic, cholecystitis, acute pancreatitis, or hepatic abscess. In some patients, larval migration causes Loeffler's syndrome, characterized by pleuritic chest pain, wheezing, fevers, and occasionally hemoptysis. This typically presents 1–2 weeks after the initial infection. In children, recurrent ascariasis can cause stunted linear growth, malnutrition, and reduced cognitive function. Diagnosis is established by the presence of *Ascaris* eggs in the feces. Early infection results in eosinophilia on CBC. Worms in gas-filled areas of

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the bowel can occasionally be seen on radiographs. Treatment is with oral albendazole in a 400 mg single dose, alternatively with mebendazole 500 mg single dose or pyrantel pamoate 11 mg/kg single dose [14, 19].

Hookworm infections are caused by two organisms, *Necator americanus* and *Ancylostoma duodenale*. Hookworms require warm weather and a moist environment to survive and are endemic in sub-Saharan Africa and Asia. Transmission is through direct contact with human skin. Once inoculated, hookworms migrate to the small bowel. The clinical presentation is mild with epigastric pain, diarrhea, and loss of appetite. A pruritic maculopapular rash at the site of entry is a clinical clue of infectious source on physical exam. Hookworms attach to the intestinal wall and secrete anticoagulants and inhibitors of platelet activators potentially resulting in a clinically significant iron deficiency anemia. Presence of hookworms on a fecal smear examination makes the diagnosis. Treatment is with a single 400 mg dose of albendazole [19].

Strongyloides stercoralis is the only nematode that can complete its entire life cycle in one human host. It is endemic throughout the tropics and subtropics. In the United States, it is found among migrant workers and endemic in the Appalachia region. The clinical presentation is usually mild, with nonspecific gastrointestinal or pulmonary symptoms and a maculopapular rash. A life-threatening hyperinfection syndrome has been associated with strongyloides, characterized by fever, chills, and anorexia with progression to multiorgan failure with ARDS. Diagnosis is via stool examination for ova or enzyme-linked immunosorbent assay (ELISA) testing. Treatment with thiabendazole or ivermectin is effective [14, 19].

Structural Diseases

Diverticular Disease

General Principles

Diverticulosis is the outpouching or herniation of the colonic wall. Colonic diverticula commonly form at vulnerable regions throughout the colon, usually in areas where the vasa recta penetrate the colonic wall. Although the exact cause is unknown, diverticulosis is thought to occur as a result of a low-fiber diet. Low fiber results in diminished stool volumes, which in turn alters the motility of the colon, thus creating higher pressures within the lumen. Diverticulosis, particularly of the sigmoid colon, is common in Western countries and has been discovered in up to 60% of patients over the age of 70. In contrast diverticulosis is less common in Asian countries and occurs predominately in the proximal colon [20].

A patient with symptomatic diverticular inflammation is said to have the diverticular disease [21]. Approximately 20% of diverticulosis patients will develop the acute diverticular disease, diverticulitis. Diverticulitis is thought to occur as a result of diverticular obstruction from colonic debris, such as a fecalith or food particle. The obstruction allows for bacterial infiltration and accumulation in the diverticula, causing inflammation [20].

Clinical Presentation

The clinical presentation of patients with diverticular disease depends on the severity of the inflammation and the presence of complications. Signs and symptoms range from colicky abdominal pain relieved with bowel movements to acute abdominal pain, fever, and leukocytosis. Other symptoms include nausea, vomiting, diarrhea, or constipation. On exam, the patient may have left lower quadrant tenderness and/or fullness [21].

Currently, there is no universally accepted clinical classification of diverticular disease; however, it can be divided into acute or chronic; acute diverticulitis can be additionally classified as uncomplicated, recurrent, and complicated [20, 21]. The classic presentation of acute diverticulitis is fever, left lower quadrant pain, and leukocytosis [20]. Recurrent diverticular disease is defined as more than one episode of diverticulitis per year [21].

Complications of diverticulitis include phlegmon, perforation, abscess, fistula, peritonitis, strictures, small bowel obstruction, and hemorrhage [20, 21].

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Diverticular disease may develop into chronic diverticular disease as a result of ongoing mucosal inflammation, and symptoms can include left lower quadrant pain, bloating, and diarrhea [20].

Diagnosis

The diagnosis of acute diverticulitis is usually made clinically; however, an abdominal computed tomography (CT) scan with IV contrast helps confirm the diagnosis if there is uncertainty [20]. Additionally, a CT scan can identify complications of diverticulitis, which would determine if a patient requires early surgical intervention [20, 21].

Laboratory studies such as a complete blood count (CBC) and basic metabolic panel (BMP) should be obtained to assess for leukocytosis and renal function/electrolyte abnormalities, respectfully [22].

Management

In general, asymptomatic diverticulosis does not require treatment; however, these patients may benefit from making certain lifestyle changes, such as increasing physical activity and adopting a high-fiber low-fat diet [21].

Antibiotic therapy is generally indicated for acute diverticulitis. Typically, broad-spectrum antibiotics with aerobic and anaerobic coverage are prescribed; and the route of administration and duration of treatment depend on disease severity [20, 21].

In patients with mild or moderate diverticulitis without signs of complicated disease (i.e., fever, peritonitis), patients can generally be treated with oral antibiotics for 7–10 days in the outpatient setting with close follow-up. Hospitalization, IV antibiotics, and bowel rest are indicated if a patient has severe diverticulitis and/or fails to improve with outpatient therapy. IV antibiotics are typically administered for 7–10 days, and oral antibiotics are recommended for an additional 7–10 days after discharge [21].

In addition to the above treatment, patients with complicated diverticulitis may require more invasive treatments, such as surgery or percutaneous drainage of an abscess [21] (Table 3).

Microscopic Colitis

General Principles

Microscopic colitis (MC) is a general term for patients with otherwise unexplained chronic watery diarrhea. Colonoscopy in these patients will reveal grossly normal mucosa; however, inflammatory changes are seen on biopsy [23, 24].

MC has two major subgroups: collagenous colitis (CC) and lymphocytic colitis (LC) [24]. These subgroups share symptoms and respond to the same treatment; however, they differ in histologic appearance; CC demonstrates thickening of the subepithelial collagen band ($\geq$10 μm), while an increased number of intraepithelial lymphocytes (IEL) is the hallmark characteristic of LC ($\geq$20 IELs/100 epithelial cells) [23].

Etiology, Risk Factors, and Associated Diseases

The etiology of MC is generally unknown; however, the development and/or severity of the disease is linked with several risk factors and certain medications. Medications associated with the development of MC include NSAIDs, PPIs (notably lansoprazole and omeprazole), ASA, lisinopril, simvastatin, paroxetine, sertraline, carbamazepine, acarbose, ranitidine, and ticlopidine [24, 25].

Risk factors for MC include female gender, increased age (average age at diagnosis is between 50 and 60), certain autoimmune diseases, malignancy (either past or present), and solid organ transplant. While it is generally unknown why females are affected more than males, some speculate MC may have a hormonal component [24].

MC also has a strong association with autoimmune disorders. Up to 30–50% of patients diagnosed with MC have at least one preexisting autoimmune disease, such as celiac disease or thyroid disease. As for other associations, a well-documented environmental risk factor for MC is cigarette smoking. It has been demonstrated that MC develops approximately 10 years earlier in active smokers [23, 24].

Clinical Presentation and Diagnosis

Patients with MC typically present with chronic, watery, non-bloody diarrhea. Other symptoms

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Table 3 Diverticulitis treatment options [20–22]

Uncomplicated diverticulitis	**Mild to moderate disease** Outpatient management with close follow-up Oral antibiotics (7–10 days) Possible combinations: Trimethoprim/sulfamethoxazole (160/800 mg po q12 hours) ***OR*** Ciprofloxacin (750 mg po q12 hours) + metronidazole (500 mg po q6 hours) ***OR*** Amoxicillin + clavulanate ER (two 1000/62.5 mg tablets po q12 hours) ***OR*** Moxifloxacin (400 mg po q24 hours) **Severe disease:** Hospitalization Bowel rest IV antibiotics (7–10 days) Possible combinations: Piperacillin/tazobactam (3.375 g IV q6 hours or 4.5 g IV q8 hours) ***OR*** Ciprofloxacin (400 mg IV q12 hours + metronidazole (500 mg IV q6 hours or 1 g IV q12 hours) ***OR*** Moxifloxacin (400 mg IV q24 hours) Oral antibiotics at discharge (7–10 days) (see above)
Complicated diverticulitis	**Abscess:** <4 cm = same as severe disease (see above) >4 cm = percutaneous drainage in addition to above **Perforation, fistulas:** Surgical intervention **Bleeding:** Colonoscopy Surgical intervention
Recurrent diverticulitis	Surgical intervention

include crampy/dull abdominal pain (common), fatigue (present in 50–60% of patients), weight loss, and fecal incontinence. The clinical presentation of MC mimics that of irritable bowel syndrome; however, MC has some additional features: nocturnal bowel movements, arthralgias, and fecal incontinence [23, 24].

A diagnosis of MC cannot be definitively made clinically. If MC is suspected, a colonoscopy with biopsy is the next step to make the diagnosis. Given that the microscopic lesions are not always continuous in MC, it is recommended that random biopsies be taken in all areas of the colon. Furthermore, to make the correct diagnosis, the biopsies should be examined by a pathologist with specialized training [24].

Treatment

Treatment is patient-dependent and should be modified based on disease severity and clinical response. Budesonide is considered first-line treatment and is highly effective at inducing clinical remission. In contrast to other glucocorticoids, budesonide undergoes high first-pass metabolism in the liver resulting in low systemic absorption. If the disease is refractory to treatment, a differential diagnosis should be reconsidered, and concurrent celiac disease or bile-acid malabsorption should be appropriately managed [23, 25] (Fig. 1).

Inflammatory Bowel Disease

General Principles

Inflammatory bowel disease (IBD) encompasses the diseases ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. The incidence of IBD has increased in almost every industrialized country over the twenty-first

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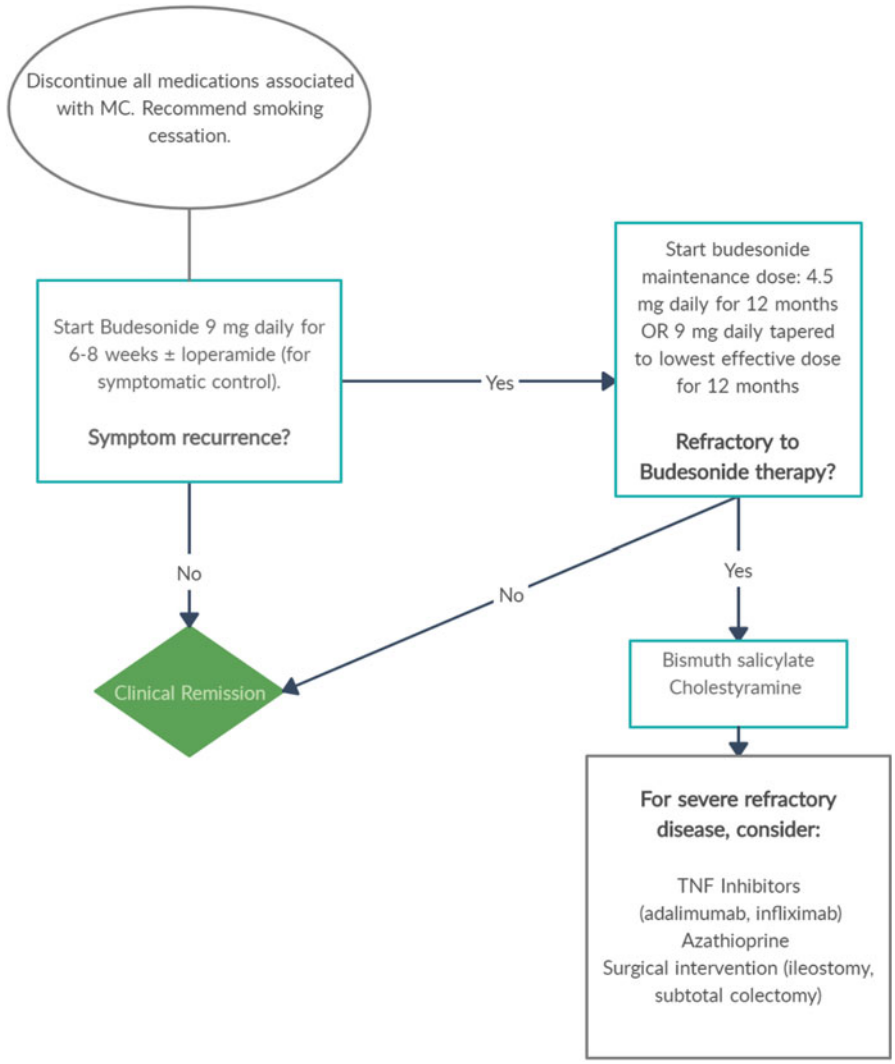


Fig. 1 Approach to MC management [23–25]

century. IBD is more common in North America and northern Europe than the rest of the world. Approximately 1.6 million Americans have been diagnosed with IBD. Disease onset is most likely between the second and fourth generations of life. It affects both men and women equally.

Although the etiology is still widely not understood, it seems to be multifactorial with genetics, host immunity, and environmental-related factors. All these factors lead to an increase in intestinal inflammation manifesting as IBD. The genetic link associated with IBD has been extensively studied over the last decade. Twin studies have shown a positive concordance of both UC and CD, and positive family history of IBD in a first-degree relative shows five times increased likelihood of developing the disease. There are several genes identified in IBD, concluding the disease is likely polygenic. Mutations in genes involved in host immunity, specifically in response to the intestinal bacterial microbiome, have been implicated, most of which lead to an abhorrent immune response. The incidence of IBD has increased in parts of Africa and Asia, where IBD used to be rare. Industrialization and the introduction of diets higher in saturated fats, processed meats, and

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Table 4 Extraintestinal manifestations of CD

Organ system	Manifestation	Incidence (%)
Bone	Peripheral arthropathy	20
Dermatologic	Erythema nodosum, oral aphthous ulcers, Sweet's syndrome	15, 10
Ocular	Episcleritis, uveitis	3–6, 0.5–3

lower fiber (especially for CD) are thought to contribute to the development of IBD. Dietary and industrialization changes may lead to a decrease in the diversity of the microbiome and overgrowth of certain bacteria leading to the development of IBD, specifically a decrease in Firmicutes and an increase in Proteobacteria and Bacteroidetes. Lastly, certain common medications have been shown to alter the microbiome: antibiotics, NSAIDs, contraceptives, and statins. The combination of environmental and host immunity factors may lead to the development of IBD in an already genetically predisposed individual [26].

Clinical Presentation

Symptoms of IBD often vary based on the location of the intestinal tract affected. The symptoms can be nonspecific but include:

- Irregular bowel habits and predominantly diarrhea, occasionally with blood or mucus
- Abdominal pain and intestinal cramping
- Fevers
- Fatigue and progressive weight loss

Crohn's Disease

CD produces transmural inflammation of the gastrointestinal tract anywhere from the mouth to the anus. The presentation can vary based on the location and severity of the disease. Classic symptoms include abdominal pain (improved with defecation), watery diarrhea, and progressive weight loss due to malabsorption. CD commonly involves the terminal ileum leading to pain in the right lower quadrant of the abdomen. Abdominal pain can be colicky, coinciding with flares and remission. These symptoms may persist for years before diagnosis. The chronic inflammatory state associated with CD can lead to penetrating fistulas or fibrostenotic obstructions due to adhesions. Fistulas are eventually present in 20–40% of patients. Enteroenteric fistulas are the most common, followed by enterovaginal fistulas in females. Intestinal strictures most commonly occur in the small bowel and may present with obstructive symptoms like postprandial nausea and vomiting. Up to one-third of patients present with perianal involvement, which indicates more severe disease and often involves more complex medical management and possible surgical interventions [26].

Up to 50% with CD will have extraintestinal manifestations (EIM) (Table 4). The pathogenesis of EIM is not well understood; however, it is hypothesized that the affected gut lining may trigger an altered immune response at extraintestinal sites. It is proposed that bacteria translocating across the leaky intestinal barrier trigger an autoimmune response, unable to differentiate bacterial epitopes from the host synovial tissue (i.e., joints and skin). There may also be a genetic predisposition to EIM based on studies examining IBD and patients with abnormal HLA complexes [27].

Ulcerative Colitis

Ulcerative colitis is characterized by inflammation of the mucosa and submucosa and is confined to the colon. Symptom severity correlates to the extent of the affected colon. Hallmark symptoms include abdominal pain, diarrhea (often with blood and mucus), and tenesmus. Symptom onset is usually acute and can be severe; therefore, a diagnosis is made in weeks, as opposed to years in CD. Complications of UC include fulminant colitis and toxic megacolon, which affects approximately 15% of patients and requires urgent evaluation and management [26]. Up to 7.5% of patients with UC are diagnosed with primary sclerosing cholangitis (PSC) during their disease. PSC is an independent risk factor for the development of colorectal malignancy in patients

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with IBD, necessitating the recommendation for annual surveillance colonoscopies once diagnosed [27].

Workup

If a physician suspects IBD, the first step is to take a good history and physical exam. A personal medical history should include the assessment of intestinal symptoms as well as extraintestinal symptoms. Nocturnal symptoms can help distinguish IBD from functional abdominal syndromes. Smoking history should be assessed, and signs/symptoms suggestive of malignancy ruled out. A family history of malignancies and IBD should be noted.

On physical exam, patients may have nonspecific tenderness to palpation of the abdomen. Clinicians may be able to palpate a mass that can indicate an intestinal abscess, phlegmon, or adhesion. A rectal exam should be performed for the identification of fissures, abscesses, fistulas, and skin tags [26].

Laboratory

Initial laboratory workup should include a CBC, CMP, vitamin D, vitamin B12, and stool studies (heme occult, microscopic examination, and stool culture). Results may reveal mild microcytic anemia, thrombocytosis, hypoalbuminemia, and vitamin D and B12 deficiencies. Stool samples are often heme positive with the presence of neutrophils and eosinophils. Stool cultures can rule out the presence of ova and parasites and *C. difficile* as infectious causes.

Inflammatory biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are nonspecific to IBD and are better for assessing disease remission rather than diagnosis. Fecal calprotectin is an inflammatory marker specific to the intestinal system; however, it can also be positive in diverticulitis, certain malignancies, cirrhosis, and with the use of NSAIDs and proton pump inhibitors (PPIs). It has a high negative predictive value and can be a useful screening tool in the assessment of chronic diarrhea, especially in the adolescent to young adult population. Recent evidence suggests peri-nuclear anti-neutrophil cytoplasmic antibody (p-ANCA) can distinguish UC from CD, whereas anti-*Saccharomyces cerevisiae* antibody (ASCA) may help distinguish CD from UC. IBD laboratory panels exist; however, these tests are expensive and are not well-validated, and positive results still require direct visualization diagnosis [26, 28].

Diagnosis

Colonoscopy, with intubation of the terminal ileum, is the primary diagnostic modality of choice in IBD. Esophagogastroduodenoscopy (EGD) is not initially recommended in asymptomatic patients. To assess for small bowel involvement, magnetic resonance imaging/magnetic resonance enterography (MRI/MRE) or computed tomography/computed tomography enteropathy (CT/CTE) is recommended. Capsule pill endoscopy can be used to aid in the diagnosis of suspected small bowel disease in CD when EGD or cross-sectional imaging is equivocal, but luminal strictures must be ruled out beforehand. Patients with IBD are likely to require numerous imaging studies throughout their lifetime; thus, several gastroenterologists prefer MRI or US (performed at specialty centers) over CT to decrease radiation risk [28].

Management

IBD is a lifelong disease characterized by periods of flare and remission. The best treatment strategies come from team-based care with frequent collaboration between primary care physicians, gastroenterologists, and surgical specialists. Most patients will require both medical and surgical interventions over their lifetimes. With advances in pharmacologic options for IBD, treatment has shifted away from symptom-based to target mucosal healing. This is especially true in CD, where chronic subclinical inflammation is present and leads to possible fistulas and stenosis, which frequently require surgical correction. Delays in diagnosis and achieving remission result in cumulative bowel intestinal damage, which can progress to fibrosis and an increase in disability and function. In UC early diagnosis and treatment can reduce the need for surgery and reduce the risk of colorectal cancer [29].

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A Stepwise Approach to Treatment

The goal of treating IBD is to prevent ongoing inflammation and promote gut healing by inducing and maintaining remission (prevent flares). Evidence shows a reduction of intestinal mucosal wall inflammation (<3 months) can reduce intestinal damage. Treatment strategies are aimed at inducing remission and objectively measuring remission maintenance.

Corticosteroids

Corticosteroids are the most effective treatment option to induce remission, but they must never be used alone. For patients with mild to moderate IBD, budesonide 9 g orally daily for 6–10 weeks is recommended. For patients with mild to severe colonic CD, prednisolone prescribed at a dose of 40–60 mg per day tapered over 4–8 weeks is appropriate. Failure to induce remission should be followed by the prompt addition of an immunomodulator [28].

5-Aminosalicylic Acids

In patients with UC and mild disease, aminosalicylates (5-ASA) are the mainstay of treatment for remission induction of active disease and flare prevention. Of the drugs available, sulfasalazine and mesalazine are equally effective and safe, though mesalazine may be better tolerated and can be used in those allergic to sulfasalazine. The dose for remission induction is 2–3 g orally per day (depending on the formulation), whereas doses of 1 g orally per day are effective in maintaining quiescence of disease activity. Rectal 5-ASA formulations are effective for left-sided colitis or proctitis and can be used alone or in conjunction with oral 5-ASA drugs. Unlike in UC, 5-ASA-based drugs are modest at best in maintaining remission in CD. Specifically, mesalazine is not recommended for induction or maintenance of remission in CD. An immunomodulator should be added to the treatment regimen if properly dosed 5-ASA medications do not achieve remission [29].

Immunomodulators

Immunomodulators, including thiopurines (azathioprine and 6-mercaptopurine) and methotrexate 15 mg (subcutaneously or orally) weekly, are the treatment of choice for moderate to severe UC and CD. Due to their prolonged onset of action (2–3 months), they should not be used to induce remission. Methotrexate is indicated for use in CD and should be reserved for patients who fail to respond to or are intolerant of thiopurines. Methotrexate is contraindicated in pregnancy and breastfeeding. Upon starting these medications, patients will require serial monitoring with a complete blood count (CBC) and liver function test (LFT). Adverse reactions include leukopenia, increased risk of infection (especially viral), and a rare, but significant risk of lymphoma and non-melanoma skin cancer. Before initiating therapy with an immunomodulator or biologic agent, patients require screening for tuberculosis (with anti-TNF therapy), hepatitis, HIV, and the presence of intra-abdominal abscesses, as treatment can reactivate these disease processes. Primary care physicians should consider concurrent consultation with a gastroenterologist if initiating treatment with an immunomodulator for IBD [29].

Biologicals

It is reasonable to consider the addition of a biological agent if disease remission is not maintained with the use of an immunomodulator alone. Monoclonal antibody (MAB) agents targeting tumor necrosis factor alpha (TNFα) and integrin have been shown to control intestinal wall inflammation. MAB therapy is indicated for moderate to severe luminal CD (adalimumab and infliximab) and moderate to severe UC (adalimumab, infliximab, and golimumab). It is also indicated in patients with debilitating EIM. Combination therapy with an immunomodulator appears to be superior to MAB monotherapy. A significant loss of response (20–40%) during the first year of anti-TNFα use is thought to be due to immunogenicity. The use of TNFα antagonists is associated with hepatosplenic T-cell lymphoma, a rare, but potentially fatal disease in young males [29].

Microbiome Therapies

Much like the concept of using fecal transplants as a treatment for *C. difficile*, researchers are investigating the use of microbiome fecal transplants in

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patients with IBD; however, this therapy is in its infancy. Preliminary studies have shown it may be helpful in the induction, but not the maintenance, of remission in UC [29].

Surgery

Surgery can be curative for patients with UC; however, because CD can affect anywhere along the alimentary tract from mouth to anus, surgery may only be a temporizing measure. It can lead to complications of obstruction from adhesions and short bowel syndrome development in the future. In UC, surgery is indicated in patients who fail or are intolerant to medical management, develop colonic perforation or toxic megacolon, or have precancerous lesions found on screening colonoscopy. Surgical options include resection of the entire colon with or without the rectum. Restorative proctocolectomy with ileal pouch-anal anastomosis and total abdominal colectomy with ileorectal anastomosis (TAC-IRA) both preserve fecal continence and do not result in permanent end ileostomy; however, the latter is infrequently performed because it preserves the rectum; therefore, the potential for persistent inflammatory symptoms and the risk of malignancy remain. TAC-IRA may be the preferred surgical option in women who wish to preserve their fertility.

In CD laparoscopic resection can be considered in patients with localized ileocecal disease who fail or relapse on medical management. Surgery may also be necessary for intra-abdominal abscesses or fistulas, once medically optimized, and if percutaneous drainage is not feasible [28].

Additional Primary Care Considerations

IBD is a lifelong disease, which requires frequent monitoring of remission and flare status. During all disease states, it is essential to encourage healthy lifestyle behaviors, optimize nutrition, ensure updated vaccination status, and monitor for drug side effects. Smoking cessation should be emphasized at every visit as smoking tobacco is strongly associated with adverse outcomes in CD and post-surgical resections. Vitamin B12, vitamin D, folate, and an iron panel should be ordered every 6 months to assess for malabsorption and supplementation as appropriate. Diets should be rich in variety, including high fiber, low processed meats, and foods. Low-fiber diets should only be advised for patients with stricturing CD. Patients who have been on prolonged or repeated doses of corticosteroids should be screened for osteoporosis with a dual-energy X-ray absorptiometry (DXA) scan and be encouraged to supplement with calcium/vitamin D. Hepatitis A and B, tetanus, diphtheria, pertussis, human papillomavirus (HPV), pneumococcal, and influenza vaccines are all recommended. Live vaccines are not to be given while patients are on immunosuppressive therapy. Patients on thiopurine medications should be advised about regular sunscreen use and should have regular skin checks. Regular endoscopy helps assess disease status but is especially crucial for dysplasia surveillance in UC [28]. Preconception counseling is especially important in women with IBD because the best pregnancy outcomes are seen in patients with disease remission at the time of conception and control of the disease throughout the pregnancy. Most medications, except methotrexate, are safe during pregnancy, while the risk of disease flare is associated with increased risk of spontaneous abortion, preterm birth, and low birth weight [30].

Malabsorption

General Principles

The term "malabsorption syndrome" has been used in the past to encompass malabsorption and maldigestion or the inability to absorb or digest nutrient or electrolytes. However, it is not a single disease, diagnosis, or process. Subclassifications include global, selective, primary, and acquired, each one specific in its pathogenesis, diagnosis, and treatment (see Table 5).

Presentation and Workup

Chronic diarrhea, due to high osmotic load, is the most common clinical manifestation of malabsorption. Diarrhea can be watery, pale, foul-

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Table 5 Malabsorption classification table

Type	Process and example
Global	Distributed mucosal involvement, multiple nutrients affected; celiac sprue
Selective	Single or limited number of nutrients involved; pernicious anemia
Primary	Secondary to congenital defects in transport systems; cystic fibrosis
Acquired	Usually surgical in nature; resections or bypass

Table 6 Malabsorption: nutrient deficiency with correlated labs with features

Common nutrients	Presentation	Lab work/imaging
Carbohydrates	Watery diarrhea, flatulence, dairy intolerance	Increased breath hydrogen, stool osmotic gap, acidic stool pH
Fat	Steatorrhea, pale and voluminous stools, limited flatulence, dermatitis, poor wound healing	Increased fractional fat excretion (>7%)
Protein	Edema, muscle wasting	Hyperproteinemia, hypoalbuminemia
Vitamin B12/Folate	Fatigue, pallor, SOB, paresthesia	Macrocytic anemia, elevated homocysteine levels, decreased B12/folate
Iron	Fatigue, pallor, chest pain, SOB, pica, tachycardia	Low serum iron and ferritin
Calcium and vitamin D	Tetany, paresthesia, pathologic fractures, fatigue	Decreased calcium, elevated alkaline phosphatase, decreased vitamin D

smelling, greasy, and of varying volume depending on the severity and classification. Other presentations can include weight loss, fatigue, flatulence, anorexia, abdominal distention, and, more rarely, abdominal pain. Workup includes a detailed history to narrow possible etiologies, including clarifying the duration of symptoms, nature of stool, type of foods causing symptoms, timing of symptoms with foods, medical history, surgical history, family history (especially in relation to celiac disease), alcohol use, and other associated symptoms.

Lab tests and imaging should be focused and based on the patient's presentation. Routine lab tests can include complete blood count, calcium, albumin, magnesium, iron studies (serum iron and TIBC specifically), vitamin B12, 25-hydroxyvitamin D, and folate. Although these are not considered diagnostic, they provide more auxiliary evidence for your diagnosis. By using the patient's clinical presentation, in combination with the laboratory findings, a specific nutrient deficiency may be isolated (see Table 6).

Some etiologies of malabsorption are clear (e.g., cystic fibrosis which can be diagnosed at birth or early in childhood), while others are not. When initial lab work and history are not sufficient to make a diagnosis, other more specific tests should be employed. The most common tests include tissue transglutaminase-IgA antibody and total IgA levels for celiac disease (sprue), fecal elastase for pancreatic insufficiency, and carbohydrate breath test for small intestinal bacterial overgrowth. Imaging and further evaluation can be warranted to confirm diagnosis and determine the extent of the disease.

Procedures and Imaging

In patients where history and lab work are inadequate to limit the diagnosis or identify the underlying cause, the physician should order/perform an upper endoscopy and colonoscopy. During these procedures the overall state of the mucosal lining is evaluated, and multiple biopsies are performed. Histologic studies are helpful in ruling out multiple conditions including Crohn's disease and ulcerative colitis. If the endoscopies are unremarkable, proceeding with specific imaging is indicated. Computed tomography (CT), magnetic resonance enterography (MRE), or an upper gastrointestinal series with small bowel follow through are all viable options. While wireless

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Table 7 Directed therapies based on diagnosis

Diagnosis	Treatments	Diagnosis	Treatments
Bile acid deficiency	Exogenous acids	Zollinger-Ellison syndrome	High-dose PPI
Small intestine bacterial overgrowth	Antibiotics (rifaximin, TMP-SMX, ciprofloxacin)	Carbohydrate intolerance (lactose deficiency)	Avoidance or exogenous enzymes
Exocrine pancreatic insufficiency/cystic fibrosis	Exogenous enzymes, managed fat intake	Ileal resection/short bowel	Cholestyramine and vitamin supplementation, small meals, and antidiarrheals
Celiac disease	Gluten-free diet		

capsule endoscopy is also available, its role is limited and should be employed by gastroenterologists for specific circumstances.

Treatment

In malabsorptive disorders the goal is to identify the deficiency and then treat the underlying cause. When treatments are not curative, the goal should be to increase the patient's quality of life with symptomatic control. Treatments for each individual etiology vary greatly, and therapies should be directed for each condition as diagnosed (see Table 7).

Diet and medication recommendations for patients with undifferentiated malabsorption and chronic diarrhea are general and based on improving quality of life. Advise patients to decrease their osmotic load with decreased sugar and sorbitol intake, especially in shortened colons. Limit diuretics use, including caffeine. When underlying disease management and diet modification are not sufficient, loperamide can be prescribed to prolong transit time and increase absorption. A tincture of opium can be utilized if loperamide is ineffective. However, care must be used as its side effects include sedation and addiction [31–34].

Irritable Bowel Syndrome

General Principles

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder occurring in approximately 9%–23% of the population worldwide. IBS is typically found in young or middle-aged adults, with a prevalence of 14% in women and 9% in men. Patients normally present with abdominal pain (usually characterized as cramping), altered bowel habits (diarrhea, constipation, or alternating between the two), bowel frequency, flatus, bowel urgency, and pain relief with defecation. The cause of IBS and its pathophysiology is still unclear. There is no identified underlying anatomic or inflammatory pathology. IBS is a clinical diagnosis and can be divided into four different subtypes. Patients commonly have psychosocial complications that may perturb gastrointestinal function and propagate symptoms. These associated psychiatric disorders include anxiety, depression, and somatization. Conditions such as fibromyalgia, functional dyspepsia, chronic fatigue syndrome, and noncardiac chest pain are also closely related to patients diagnosed with IBS.

Clinical Presentation

Patients with the hallmark symptoms of chronic bowel pain (especially if relieved by defecation) and altered bowel habits should be suspected to have IBS. Patients may also experience lack of appetite, nausea, excessive flatus, bowel urgency, and food intolerance. Symptoms such as weight loss, fever, nocturnal symptoms, age of onset >50, melena, progressive pain, and cachexia are less likely to be indicators of IBS. The physical exam is typically normal although some may exhibit mild abdominal tenderness to palpation and some stool burden may be felt in IBS-C patients.

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Diagnosis

IBS is a diagnosis of exclusion, and a thorough elimination of organic causes should be performed. Lab work should include obtaining a CBC, CMP, TSH, fecal calprotectin (or lactoferrin), stool testing for *C. difficile* toxin, giardia, ova and parasites with culture, and serologic testing for celiac disease. It is also important to complete age-appropriate colorectal cancer screening and, if presenting with constipation, an abdominal radiograph. Colonoscopy, outside of age-related screening, is reserved for patients with normal lab work but a family history of inflammatory bowel disease and/or colon cancer. Patients with abnormal lab work (anemia, elevated inflammatory markers, or electrolyte disturbances) and concerning symptoms such as hematochezia, melena, and weight loss should also be considered for colonoscopy. The most widely accepted diagnostic standard is currently the Rome criteria (Table 8).

When possible, subclassification is helpful for determining treatment. The most commonly accepted subtypes are IBS-D (diarrhea predominant), IBS-C (constipation predominant), IBS-M (mixed diarrhea and constipation), and IBS-A (alternating diarrhea and constipation). There are currently arguments to include a pain predominant subtype as well.

Management

The foundation of successful management of IBS is a strong relationship between patient and physician. It is also key in setting realistic expectations. After diagnosis, the patient should be reassured that although the disease is chronic, it does not increase risk of malignancy and does not have a serious pathological course. Treatment should be individualized and based on subtype if possible. A comprehensive diet history should be examined to identify trigger foods. Patients may benefit from adherence to a low FODMAP diet along with avoidance of gas-producing food. Data support the intake of additional dietary fiber in patients with IBS-C, although it may increase bloating and gas. Probiotics and regular exercise may also be beneficial in overall IBS symptom reduction. Complementary and alternate medicine (CAM) such as cognitive behavioral therapy, mind-body therapies, acupuncture, and hypnotherapy should be explored. However, the current CAM research leaves a void for more robust and significant studies evaluating those modalities.

Pharmacological therapies are broad, and benefits may vary greatly between patients. Treatment should be based on predominant symptoms, and changes should occur over 2–4-week intervals. General medications include anticholinergics (dicyclomine and hyoscyamine), tricyclic antidepressants (amitriptyline, imipramine), serotonin 5-HT3 receptor antagonists (alosetron), guanylate cyclase C agonists (linaclotide), and antispasmodics (peppermint oil, pinaverium, trimebutine, cimetropium/dicyclomine). IBS-C can be directed toward chloride channel activators (lubiprostone) when symptoms are resistant toward osmotic laxatives. In IBS-D antidiarrheals (loperamide, diphenoxylate) are used as the initial treatment with bile acid sequestrants as second-line therapy. Treatment should be based on the predominant symptom, and changes should occur over 2–4-week intervals. In IBS without constipation, with significant bloating, a 2-week trial of rifaximin can be used; however antibiotics are not routinely recommended [34–37].

Table 8 Rome criteria

Recurrent abdominal pain for at least 1 day per week in the last 3 months, as an average, and association with two or more of the following:	1) Related to defecation 2) Associated with a change in stool frequency 3) Associated with a change in stool form (appearance)

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Diseases of the Pancreas

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Douglas J. Inciarte and Daniel Ramon

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Pancreatic disease causes significant health issues ranging from pancreatitis and pancreatic cysts to cancer. To reduce this burden, family physicians need a systematic approach to evaluation and treatment.

Acute Pancreatitis

Background

Acute pancreatitis, an inflammatory disease of the pancreas, is one of the most common gastrointestinal disorders requiring hospitalization. It has a reported annual incidence of 13–45 cases per 100,000 persons [1]. Acute pancreatitis is hypothesized to be caused by unregulated activation of trypsin within pancreatic acinar cells, leading to the autodigestion of the gland and local inflammation [2].

Etiology

The most common causes are gallstones (40–70%) and alcohol use (25–35%) [3]. In patients greater than 40 years of age, a pancreatic tumor can be considered as a possible cause. For the remainder of patients for whom no etiology is established (15–25%), this is referred to as idiopathic acute pancreatitis.

Diagnosis

Acute pancreatitis is diagnosed when two out of three of the following criteria are present: (1) abdominal pain consistent with the disease, (2) serum amylase and/or lipase greater than three times the upper limit of normal, and (3) characteristic findings from abdominal imaging [3].

Clinical Features

Patients with acute pancreatitis typically describe a history of constant epigastric or upper quadrant pain, with radiation to the back, chest, or flanks. On examination, the upper abdomen can be tender, and bruising caused by bleeding due to pancreatic necrosis can be seen in the periumbilical region (Cullen's sign) and flanks (Grey Turner's sign). Also, extension of inflammatory exudates to the diaphragm may result in shallow respiration [2].

Laboratory Tests

For initial laboratory studies, serum amylase alone cannot be used reliably for the diagnosis. Serum lipase is more specific for acute pancreatitis and remains elevated longer than amylase. However, serum amylase and lipase may be high in the absence of acute pancreatitis. Another important laboratory marker in assessing severity is C-reactive protein (CRP), an acute phase reactant that reaches a peak concentration 72–96 hours after symptom onset. It is significantly higher in patients with necrotizing disease [4]. Genetic testing may also be considered in young patients (less than 30 years old) if no cause is evident and a family history of pancreatic disease is present [3].

Imaging

A transabdominal ultrasound should be performed in all patients with acute pancreatitis to assess for gallstones. While a contrast-enhanced CT (CECT) provides greater than 90% sensitivity and specificity for the diagnosis of acute pancreatitis, its routine use is not needed. Magnetic resonance imaging (MRI) is comparable to CECT in the early assessment of acute pancreatitis, and MRI employing magnetic resonance cholangiopancreatography (MRCP) has the additional advantage of diagnosing choledocholithiasis and pancreatic duct disruption. MRI can be substituted for CECT in patients with contrast

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allergy and renal insufficiency (can perform without gadolinium contrast and still diagnose pancreatic necrosis). Either follow-up CECT or MRI is useful for patients lacking clinical improvement, with clinical deterioration, or when invasive intervention is considered [3, 5].

Differential Diagnosis

The differential includes cholecystitis, cholelithiasis, cholangitis, choledocholithiasis, peptic ulcer disease, gastritis, chronic pancreatitis, acute or chronic alcohol consumption, perforated ulcer, early appendicitis, bowel obstruction, mesenteric ischemia, gastroenteritis, post-traumatic injury, or malignancy [6].

Treatment

Severity Prediction

Most episodes of acute pancreatitis are mild and self-limited, requiring brief hospitalization. Approximately 20% of patients develop severe disease with local and extrapancreatic complications involving hypovolemia and multiple organ dysfunction. Therefore, risk stratification of acute pancreatitis is important. The revised Atlanta classification now divides acute pancreatitis into three categories: (1) mild, no organ failure or local complications; (2) moderate, local complications and/or transient organ failure (less than 48 hours), the presence of shock, gastrointestinal bleeding, pulmonary insufficiency, or renal failure; and (3) severe, persistent organ failure (greater than 48 hours). Various scales can assess injury to extrapancreatic organs – the greater the number of organs injured, the greater the score [2, 3].

Fluid Therapy

Early aggressive intravenous hydration is most beneficial during the first 12–24 hours to correct third spacing and maintain an adequate intravascular volume. Fluid requirements should be reassessed at frequent intervals – within 6 hours of admission and for the next 24–48 hours – using caution in patients with cardiovascular, renal diseases, or other comorbidities [3].

Nutrition

Patients with mild-to-moderate acute pancreatitis do not require nutritional support and can start oral feeding once abdominal pain decreases and inflammatory markers improve. For patients with severe acute pancreatitis, necrotic pancreas, or organ failure, enteral nutrition should be started within 48 hours: [5] nasogastric or nasojejunal feeding is comparable in efficacy and safety [7]. Avoid parenteral nutrition due to risk of infections and other line-related complications, unless the enteral route is not available, not tolerated, or not meeting caloric requirements [3].

Pain Management

Adequate analgesia is important for patients with acute pancreatitis. For mild cases, non-opioid drugs may be enough to manage pain. Narcotic agents are often needed for severe cases [8].

Antibiotics

Intravenous antibiotic prophylaxis is not recommended for the prevention of complications in acute pancreatitis. In severe pancreatitis with infected necrosis, coverage for gram-negative organisms (using carbapenems, quinolones, and metronidazole) is strongly recommended as soon as possible after a severe attack [5].

Causative Therapy

Early endoscopic retrograde cholangiopancreatography (ERCP), preferably within 24 hours, is indicated for concomitant cholangitis, significant persistent biliary obstruction, or severe biliary pancreatitis without biliary sepsis or obstruction. It is not indicated in mild pancreatitis of suspected or proven biliary etiology in the absence of biliary obstruction [3]. For mild gallstone-associated acute pancreatitis, early cholecystectomy (preferably during the same hospitalization) is recommended, and no later than 2–4 weeks after discharge. In patients with severe gallstone-associated acute pancreatitis, cholecystectomy should be delayed until there is sufficient resolution of the inflammatory response and clinical recovery [3].

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Complication Management

Pancreatic necrosis is the most severe complication as it is frequently associated with pancreatic infections. It occurs when a local area of nonviable parenchyma becomes infected with bacteria originating from the gut, leading to infected necrosis, pancreatic abscess, or infected pseudocysts. A pseudocyst is a pancreatic fluid collection that has been enclosed by a wall of granulation tissue that results from pancreatic duct leakage [2]. In acute necrotizing pancreatitis, the findings of necrosis on CECT and a persistent severe inflammatory response syndrome (SIRS) should prompt fine needle aspiration (FNA) with gram stain and culture to differentiate sterile and infected necrosis. For patients with sterile necrosis in the first week, mortality is between 10% and 40%. Surgery is indicated for the presence of massive pancreatic necrosis (greater than 50%) with a deteriorating clinical course and in patients with progression of organ dysfunction or no signs of improvement. In infected necrosis, after 3 weeks, mortality ranges between 20% and 70%. Antibiotics should be used for treatment first, and if patients remain ill and infected necrosis has not resolved, then minimally invasive necrosectomy is recommended [3].

Chronic Pancreatitis

Background

Chronic pancreatitis is a progressive inflammatory change of the pancreas that results in permanent structural damage, leading to impairment of exocrine and endocrine function [9]. It has a reported annual incidence of 5–12 cases per 100,000 persons, which accounts for more than 120,000 outpatient visits and 50,000 hospitalizations annually [10].

Etiology

Most cases are due to alcohol abuse, ductal obstruction, genetic mutations, systemic disease, autoimmune pancreatitis, tropical pancreatitis, and idiopathic pancreatitis [11, 12]. Cigarette smoking has been found to be an independent, dose-dependent risk factor for acute and chronic pancreatitis [13].

Diagnosis

Clinical Features

The primary clinical manifestations are abdominal pain and pancreatic insufficiency. The abdominal pain is typically epigastric, radiates to the back, worsens postprandially, and may be alleviated with leaning forward. This pain may occur sporadically but become more continuous as the condition progresses. Clinically significant fat and protein deficiencies do not occur until over 90% of pancreatic function is lost [14]. At variable states of progression, this may result in steatorrhea, indigestion, weight loss, and malaise. While the classic triad of pancreatic calcifications, steatorrhea, and diabetes mellitus strongly suggests the diagnosis of chronic pancreatitis, most cases are challenging to identify given the potential absence of symptoms and normal laboratory or imaging studies in over 20% of cases [15].

Laboratory Tests

Since chronic pancreatitis is a patchy, focal disease that leads to minimal increase in pancreatic enzymes in the blood, serum concentrations of amylase and lipase are usually normal or may be slightly elevated. Significant fibrosis can also result in decreased abundance of these enzymes within the pancreas. Thus, pancreatic enzyme levels should only be used when suspecting acute pancreatitis and not chronic pancreatitis. While complete blood counts, electrolytes, and liver function tests tend to be normal, elevations of serum bilirubin and alkaline phosphatase may suggest intrapancreatic compression of the bile duct. Markers of autoimmune chronic pancreatitis include an elevated ESR, IGG4, rheumatoid factor, ANA, and anti-smooth muscle antibody titer [16]. Direct pancreatic function testing for secretin with suggestive clinical features can also be used to diagnose chronic pancreatitis. However, this test is invasive, usually done under fluoroscopy, and not readily available [17]. Fecal elastase is also thought to suggest exocrine deficiency and may be used to evaluate steatorrhea [18].

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Imaging

Diagnosis can be confirmed by pancreatic calcifications on imaging (abdominal plain film or CT) or a pancreatogram revealing beading or ecstatic branching of the main pancreatic duct [14]. When comparing imaging studies, the sensitivity and specificity of ultrasound for the diagnosis of chronic pancreatitis are 60–70% and 80–90%, respectively, which is slightly less than corresponding values for CT, which are 75–90% and 85%, respectively [19]. These values drop in early disease for both forms of imaging. Magnetic resonance cholangiopancreatography (MRCP) is becoming the diagnostic test of choice since it can demonstrate calcifications and pancreatic duct obstruction while avoiding risks of radiation without the invasiveness of the prior test of choice, endoscopic retrograde cholangiopancreatography (ERCP). Endoscopic ultrasonography (EUS) may also be as sensitive as ERCP when done by a highly skilled gastroenterologist [15] and provide additional procedures that may detect earlier disease missed by approaches aforementioned [20].

Classification

The Cambridge classification system divides severity of disease into category I equivocal changes, category II mild to moderate, and category III considerable changes based on ERCP findings [21].

Differential Diagnosis

Due to its nonspecific presentation, it is important to differentiate from other diseases such as pancreatic cancer, acute pancreatitis, pancreatic endocrine tumors, pancreatic duct stones, pseudocysts, hepatobiliary disease, systemic autoimmune disease, or lymphoma [14].

Treatment

Treatment for chronic pancreatitis focuses on pain management, correction of pancreatic insufficiency, and management of complications. Recommendations begin with alcohol and tobacco cessation and consumption of small low-fat meals [22]. If pain is persistent, pancreatic enzyme supplements can be initiated. Oral intake should be avoided to minimize pancreatic stimulation. Analgesics with opioids and/or NSAIDs can be used. Adjuvant therapy with neuropathic agents (i.e., gabapentin or pregabalin) and tricyclic antidepressants (i.e., amitriptyline and nortriptyline) may provide additional pain control [23, 24]. Pancreatic enzyme supplementation is based on suppression of pancreatic exocrine secretion, and while several studies do show benefit from placebo effect, it has also been shown with some evidence as a reasonable addition to measures above for patients with persistent pain [25]. In cases of refractory pain, EUS may be diagnostic and therapeutic, with procedures such as celiac plexus block and celiac plexus neurolysis and EUS-guided drainage of pancreatic fluid collections [20]. Extracorporeal shock wave lithotripsy in conjunction with EUS can help remove larger or impacted pancreatic ductal stones [26]. Finally, surgery is reserved for refractory pain. Although medical treatment and endoscopic interventions are primarily offered to patients with chronic pancreatitis, approximately 40–75% will ultimately require surgery. Although pancreaticoduodenectomy has been considered the standard surgical procedure, its high postoperative complication and pancreatic exocrine and/or endocrine dysfunction rates have led to a growing popularity for duodenal-preserving pancreatic head resection such as the Frey procedure [27]. Nutritional deficiencies have been documented in advanced disease, including fat-soluble vitamins, vitamin B12, zinc, calcium, magnesium, thiamine, and folic acid [28]. Monitoring levels and supplementing accordingly along with screening for diseases or symptoms associated with these deficiencies are also important.

Pancreatic Cysts

Background

In the past two decades, the prevalence of pancreatic cysts diagnosed in US adults has dramatically increased [29]. In the USA, 20% of patients who undergo MRI for nonpancreatic diseases are found to have a pancreatic cyst [30]. The most common include pseudocysts, serous

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cystadenomas (SCA), mucinous cystic neoplasms (MCN), and intraductal papillary mucinous neoplasms (IPMN) [31]. Distinguishing SCA from MCN and IPMN is key as SCA is benign while MCN and IPMN are potentially or overtly malignant lesions.

Clinical Features

There is no typical presentation or physical exam findings. IPMNs are more likely to be found in males while SCA and MCN are mostly seen in women. There is no alcohol abuse or history of pancreatitis in SCA, MCN, or IPMN. Malignancy potential is rare in SCA, moderate to high in MCN, and low to high in IPMN [31].

Diagnosis

Transabdominal ultrasound has difficulty visualizing the entire pancreas and is highly operator dependent. The preferred imaging options are CT, MRI, and endoscopic ultrasound. ERCP can be used but it can only help diagnose IPMN and is an invasive test. MRI has been considered superior to CT for characterizing morphological features of pancreatic cysts [32]. However, CT was shown to have an accuracy rate of 80% for discriminating between mucinous and non-mucinous cysts [33], while MRI had less interobserver agreement [32]. EUS provides another option if CT and MRI imaging are not diagnostic, particularly in showing internal septa, mural nodules, solid masses, vascular invasion, and lymph node metastases. EUS can be combined with FNA of the lesion for collection and analysis of fluid and solid components. Cyst fluid with elevated carcinoembryonic antigen distinguishes mucinous from non-mucinous cysts but cannot determine malignancy potential [34]. Cyst fluid cytology can be helpful, but the fluid often has low cellularity. Because expertise in this procedure and technique is not readily available, consult with a local radiologist and endoscopist to determine the best locally available imaging approach.

Management

The initial steps are to assess patient symptoms and determine the cyst size, location, and presence of main branch involvement. If the patient has no symptoms, cyst <1 cm with no solid components or thickened cyst walls, main duct <5 mm with no abrupt caliber changes, and no mural nodule, then imaging surveillance in 2–3 years is recommended. Further EUS is not needed. If the patient has obstructive jaundice with a cystic lesion in the head of the pancreas, enhancing solid component within the cyst, or main pancreatic duct >10 mm, then surgical resection should be considered. If the cyst is >3 cm, there are thickened cyst walls, the main duct is 5–9 mm, a mural nodule is present, or the main duct has abrupt caliber changes with distal pancreatic atrophy, then the patient should undergo EUS to further define the lesion [34].

Intraductal Papillary Mucinous Neoplasm

First described in the mid-1980s, IPMN is a cystic neoplasm of the pancreas – a slow growing tumor with malignant potential. There are three types of IPMN: main duct, branch duct, and mixed type. Main duct IPMN features segmental or diffuse dilation of the main pancreatic duct of >5 mm without other causes of obstruction. Because the rate of malignancy is very high (up to 70% in reported surgical series), in surgically fit patients, the recommendation is for surgical removal of the affected portion of the pancreas or entire pancreas (total pancreatectomy) if the entire duct is involved [33]. Branch duct IPMNs may be found in various locations throughout the gland and are seen with equal frequency in both genders. Their management is challenging and lifetime risk of malignancy is not entirely known. There is no medication to treat these cysts – only options are surveillance and surgical removal. Important factors to consider include the patient's age, symptoms, the size of the cyst, and whether or not there is a solid component or mural nodule.

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Mucinous Cystic Neoplasm

MCNs are defined by the presence of ovarian stroma and are usually located in the pancreatic body and tail. Cancer is very rare in MCN <4 cm without mural nodules [31, 34]. It is most commonly diagnosed in middle-aged women. In surgically fit patients resection is routinely recommended, while observation is recommended for elderly frail patients. Surgical resections should be done at high-volume institutions, generally those that perform 15 or more pancreatic resections annually. These institutions have reported decreased mortality, hospital length of stay, and overall cost compared to low-volume institutions [35].

Pancreatic Cancer

Background

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the USA [36]. The incidence is equal in both genders but slightly higher in African Americans compared to Caucasians [37]. Over 90% of these cancers are pancreatic ductal adenocarcinomas (PDAC). There are several risk factors associated with the development of PDAC: tobacco use, alcohol use, obesity, and type 2 diabetes for five or more years. Routine screening for pancreatic cancer in asymptomatic adults who are at average risk is not recommended due to lack of mortality benefit [35]. However, in the office a clinician can consider screening individuals from families with known genetic defects predisposing them to pancreatic cancer or with familial pancreatic cancer. Although, there is insufficient evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma. The US Preventive Service Task Force recommends against screening for pancreatic cancer in asymptomatic adults [38].

Clinical Features

Abdominal pain, jaundice, pruritus, dark urine, and acholic stools may all be presenting symptoms because of obstruction within the biliary tree [39]. Nonspecific findings from cancers of the pancreatic body or tail include unexplained weight loss, anorexia, early satiety, dyspepsia, nausea, and depression [40]. Also, a sudden onset of atypical type 2 diabetes (a thin adult 50 years or older) that is difficult to control suggests pancreatic cancer [41]. Patients may present in early stages with normal exams or advanced disease with manifestations of liver involvement such as abdominal tenderness, jaundice, and cachexia. A nontender, distended, palpable gallbladder in a jaundiced patient (Courvoisier's sign) is 83–90% specific but is only 26–55% sensitive for a biliary obstruction due to malignancy [39]. Advanced pancreatic cancer, like other abdominal malignancies, can be associated with recurring superficial thrombophlebitis (Trousseau's sign) or left supraclavicular lymphadenopathy (Virchow's node). Subcutaneous areas of nodular fat necrosis (pancreatic panniculitis) may be evident in rare cases [42].

Diagnosis

CT is the gold standard for diagnosing and staging patients with pancreatic cancer [43]. A pancreas protocol CT involves triphasic (i.e., arterial phase, late phase, and venous phase) cross-sectional imaging that allows for enhancement between the parenchyma and adenocarcinoma. When CT is not possible (i.e., not available, contrast allergy, etc.), MRI with contrast can be used for diagnosis and staging. If a pancreatic mass is identified, subsequent EUS and FNA are indicated. If no mass is identified and no evidence of metastatic disease is present, further EUS or ERCP is indicated [35]. The most common serum tumor marker used for PDAC is carbohydrate antigen (CA) 19-9, which is expressed in pancreatic and hepatobiliary disease. In symptomatic patients, it can help confirm the diagnosis and predict prognosis and recurrence after resection [35]. However, CA 19-9 is not tumor specific and therefore is not a sufficient individual screening tool for asymptomatic patients [44].

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Staging

Once a mass is identified and FNA confirms tissue diagnosis, EUS can determine the tumor size and extent of lymph node metastases and assess for portal venous system involvement to complete the staging [35]. In addition to EUS, chest CT and serum liver enzyme tests are useful to determine surgical candidacy [35]. A multidisciplinary team with expertise from surgery, diagnostic imaging, pathology, interventional endoscopy, and medical and radiation oncology is highly recommended to define surgical candidates [35].

Management

Surgical resection is the only potentially curative treatment for PDAC. Around 15–20% of patients are candidates for pancreatic resection, but only around 20% of those who undergo surgery survive to 5 years [35]. Although postoperative mortality is less than 5%, the median survival is still only 12–19 months [35]. Pancreatic resections should be done at high-volume institutions, generally those that perform 15 or more pancreatic resections annually [35]. The classic operation for resection of a carcinoma of the head of the pancreas is a pancreaticoduodenectomy (Whipple procedure). For surveillance in patients with resected pancreatic cancer, expert consensus recommends history and physical examination every 3–6 months for 2 years and then annually [45]. Monitoring for recurrence with CA 19-9 levels, CT scans, and EUS every 3–6 months can also be considered, although evidence is limited that earlier treatment improves patient outcomes [46]. Over 80% of patients present with unresectable disease. Some studies have addressed the use of chemoradiation with or without chemotherapy to convert unresectable disease status to resectable. Post-resection, these patients have similar survival rates as those initially determined to be resectable [35]. The primary treatment for advanced pancreatic cancers is palliative care (i.e., adequate nutrition and pain control), which may have some effect on survival.

Exocrine Pancreatic Insufficiency

Background

Exocrine pancreatic insufficiency (EPI) is a disease characterized by deficiency of the exocrine pancreatic enzymes, resulting in maldigestion. The pathophysiological mechanism for EPI involves pancreatic parenchymal damage, pancreatic duct obstruction, or loss of sites of secretin and cholecystokinin secretion in the gastrointestinal tract [48].

Etiology

The most common causes of EPI are chronic pancreatitis, cystic fibrosis, pancreatic cancer, pancreatic resection, gastric or small bowel resection, inflammatory bowel disease, celiac disease, and diabetes mellitus [47]. The prevalence of EPI is higher in type 1 diabetes (26–57%) compared with type 2 diabetes (20–36%).

Clinical Features

Clinical symptoms associated with EPI include steatorrhea (greasy, foul-smelling stools), weight loss, increased flatulence, and abdominal pain. Deficiency of the fat-soluble vitamins (e.g., vitamins A, D, E, and K) can lead to impaired night vision, decreased bone mineralization, coagulation problems, and ataxia and peripheral neuropathy [48]. Because the exocrine pancreas has a large functional reserve capacity, clinical symptoms may not manifest until exocrine pancreatic function is $<10\%$ of normal.

Diagnosis

No single widely available test allows diagnosing EPI accurately. Diagnosis of EPI requires the evaluation of symptoms, nutritional markers, and a pancreatic function test [49]. Early diagnostic studies relied on direct pancreatic function tests (i.e., those involving collection and analysis of

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secretions directly from the duodenum or pancreatic duct), including the secretin-pancreozymin and Lundh tests, which remain the most sensitive and specific methods for assessing exocrine pancreatic function. Direct tests, however, are limited by their cost, duration, and invasive nature, which involve endoscopic aspiration or tube aspiration of secretions from the duodenum for several hours [48]. During the past 20 years, the use of noninvasive indirect methods, such as fecal elastase, has become more common. Evidence suggests the fecal elastase-1 (FE-1) test is reliable for the evaluation of pancreatic function in many pancreatic and nonpancreatic disorders. Fecal elastase, measured by enzyme-linked immunosorbent assay, has a good sensitivity for moderate EPI (75%) and high sensitivity for severe EPI (95%), and has a higher specificity (79–96%) compared with the direct tests [50].

Treatment

Patients with abnormal fecal fat excretion, steatorrhea, and/or weight loss are considered candidates for pancreatic enzyme replacement therapy (PERT). Although there is a lack of long-term trials assessing the effect of PERT on patient survival, PERT has been shown to improve digestion, symptoms, nutritional status, and quality of life of patients with EPI [49].

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Diseases of the Liver

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David T. O'Gurek

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The liver as the largest solid organ in the body carries out a large number of critical functions, including the manufacture of essential proteins, metabolism of fats and carbohydrates, and elimination of harmful waste products, alcohol, certain medications, and environmental toxins. Therefore, diseases of the liver encompass a wide variety of clinical conditions with intrahepatic and extrahepatic manifestations and complications. These also range from acute, self-limited presentations to fulminant disease with rapid liver failure to chronic, low-level disease and also to chronic liver disease that progresses slowly over time. While the history and physical signs of this broad range of clinical disorders are quite similar, often with nonspecific findings with broad-range differentials, laboratory evaluation is critical to sorting through these disease processes. It is critical for family physicians to have an understanding of liver pathology and the laboratory assessment of the hepatic system.

The term "liver function test" is often a misnomer used to describe a variety of tests that assess hepatic synthetic function (e.g., serum albumin, prothrombin time), excretory function (e.g., serum bilirubin, direct bilirubin), necroinflammatory activity (e.g., alanine aminotransferase or ALT/SGPT, aspartate aminotransferase or AST/

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Table 1 Uncommon causes of chronic liver disease and cirrhosis

Disease	Description	Diagnostic testing
Autoimmune hepatitis	Hepatic inflammation of unclear cause with hepatitis: hypergammaglobulinemia, and liver-associated autoantibodies; 2 subtypes of the disease; treatment usually with immunosuppression	Antinuclear antibody (ANA); anti-smooth muscle antibody
Alpha-1 antitripsin deficiency	Genetic disorder causing metabolic liver disorder in children; affects both hepatic and pulmonary systems	Alpha-1 antitripsin activity
Cystic fibrosis	Autosomal recessive disorder most commonly affecting Caucasian population; cirrhosis with portal hypertension common	Sweat chloride testing
Hemochromatosis	Autosomal recessive disorder resulting in dysregulation of iron absorption and resulting in iron toxicity to liver and other tissues; "bronze diabetes"	Transferrin saturation
Primary biliary cirrhosis	Female predominance; often asymptomatic; diagnosed with persistently elevated signs of cholestasis, normal biliary imaging and presence anti-mitochondrial antibody	Anti-mitochondrial antibody
Wilson's disease	Genetic disorder disrupting copper attachment to ceruloplasmin and resultant defective biliary secretion; Kayser-Fleischer rings on ophthalmologic exam; treatment with D-penicillamine	Ceruloplasmin

SGOT, and γ-glutamyltransferase or GGT), and cholestasis (alkaline phosphatase). While these tests can aid in the correct identification of liver disease, a single elevation must be confirmed with subsequent testing. Furthermore, normal or minimally abnormal tests do not preclude the presence of significant liver disease or possibly advanced disease or cirrhosis. While these tests will demonstrate liver disease, they are nonspecific and require specific testing based on risk assessment, history, and laboratory evaluation directed at specific etiologies.

The major causes of liver disease include infectious hepatitis, excessive alcohol usage, and toxic hepatopathy from drugs or other substances; however, less common metabolic abnormalities can also result in chronic liver disease and cirrhosis (see Table 1). This chapter will review the more common causes and their associated complications.

Viral, Alcoholic, and Drug-Induced Liver Disease

Hepatitis A

Hepatitis A virus (HAV) is an enveloped RNA agent classified as a picornovirus that is a common worldwide disease affecting the liver, spread through fecal-oral contamination with occasional outbreaks through food sources or within communities with specific risk factors. It can range in severity from an asymptomatic infection to a severe illness lasting several months; however, it is most commonly an acute, self-limited disease. Those at risk for worsening disease include the elderly as well those with chronic hepatitis B or hepatitis C with cirrhosis [1].

Clinical Presentation and Diagnosis

History should be targeted at collecting the chronology of symptomatology. The manifestations of HAV vary by age. While the manifestation in children is typically silent or subclinical, adults often present with signs and symptoms. With an average incubation period of about 30 days, HAV causes a prodrome of generalized fatigue, anorexia, nausea, vomiting, and fever which typically abate with the onset several days to a week later of jaundice with dark urine, acholic stools, and diffuse pruritis [2]. Clinical suspicion particularly for HAV infection is increased if there are specific risk factors by history including exposure to HAV in the household or close contact, exposure to raw vegetables or fruit or other uncooked or undercooked foods, exposure to drinking water that is not sanitized, or travel to areas endemic for HAV [3].

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Despite clinical suspicion, the symptoms are indistinguishable from other forms of viral hepatitis and other possible liver or biliary conditions, and therefore, laboratory evaluation is necessary for diagnosis. Laboratory findings often demonstrate transaminitis followed by elevated total and direct bilirubin and elevated alkaline phosphatase levels. With any type of viral hepatitis, alanine transaminase (ALT) is typically higher than the aspartate transaminase (AST), and the range for both in HAV infection is typically between 500 and 5000 U/L [4]. Diagnosis is confirmed with detection of serum immunoglobulin M (IgM) anti-HAV antibodies, which typically becomes positive within 5–10 days of infection, concurrently with onset of jaundice. This will remain positive for 4–6 months following acute infection and therefore can be used to determine whether illness which has resolved was related to HAV. Total anti-HAV (IgM and immunoglobulin G) or immunoglobulin G (IgG) levels are checked to confirm immunity or past exposure and will remain positive for a patient's lifetime.

Management

The treatment of HAV infection is solely supportive, and hospitalization is reserved for patients with significant dehydration requiring parenteral fluid resuscitation or those with complications. Patients should be advised not to return to school or work until fever and jaundice have subsided, and hepatotoxic agents such as alcohol or medications should be avoided during the acute illness. The best treatment strategy for HAV infection remains a preventive strategy with immunization.

Prevention

The prevention of HAV infection begins with the practice of sanitary practices such as hand washing, heating foods appropriately, and avoiding water and foods from endemic areas. Preexposure prophylaxis with vaccination is the most widely used prevention strategy with the recommendation that all children should receive the hepatitis A vaccine as part of routine childhood immunizations, beginning the series between 12 and 23 months of age which includes a two-vaccine series with one immunization and a repeat dose 6 months later. Additionally, those at increased risk including those traveling to endemic areas (available at http://www.cdc.gov/travel), men who have sex with men (MSM), people who inject drugs (PWID), people with chronic liver disease such as hepatitis B or hepatitis C, people experiencing homelessness, people treated with clotting-factor concentrates, parents adopting children from endemic areas, and those that work with HAV-infected animals or in HAV research labs should also receive vaccination [5–7].

Postexposure prophylaxis is available if a healthy individual has been exposed to HAV within the past 2 weeks as prophylaxis efficacy beyond this time is not well known. Hepatitis A vaccine is recommended for persons aged $\geq$ 12 months for PEP, and providers may also administer immunoglobulin (IG) to adults aged $>$ 40 years, if indicated [8]. Infants aged $<$ 12 months and persons for whom the vaccine is contraindicated should receive IG. Indications for postexposure prophylaxis include previously unvaccinated household or sexual contacts with confirmed disease; unvaccinated staff and attendees of child care centers with one or more cases in the center or two or more household cases of attendees; food handlers in facility with confirmed case; and immunocompromised persons (congenital or acquired, HIV infection, chronic renal failure, transplant recipients, persons on immunosuppressive drugs or biologics; and those with chronic liver disease) [5, 8].

Hepatitis B

Hepatitis B virus (HBV) is an incompletely double-stranded DNA virus belonging to the family of hepadnaviruses that is spread through contact with blood, semen, or other bodily fluid of an individual infected with HBV. The HBV has 10 genotypes (A through J) and more than 30 subtypes. Dissimilar to HAV, HBV causes both an acute illness as well as a chronic disease state. Although anyone can become infected with HBV, those at greater risk include individuals with multiple sexual partners, individuals with other sexually transmitted infections, MSMs, PWID, those living with someone with chronic HBV, infants born to infected mothers,

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individuals exposed to blood through their work, patients on hemodialysis, and those traveling to countries with moderate to high rates of HBV infection.

Clinical Presentation and Diagnosis

The history and presenting symptoms may vary depending upon the current state of the disease process whether in its acute phase or chronic phase. Most cases of acute hepatitis B are asymptomatic, and those with symptoms are more likely to be adults or over the age of 5. The average incubation period of HBV is 75 days, longer than that of HAV, and then patients proceed to have a prodrome with symptoms similar to that of HAV with fever, malaise, anorexia, and nausea followed by jaundice, darkening of the urine, and right upper quadrant pain.

During acute infection, elevations occur in the transaminases, both ALT and AST, with a typically higher elevation in ALT compared to AST. The alkaline phosphatase and total and direct serum bilirubin levels may be normal in someone presenting with anicteric hepatitis. As these tests are nonspecific markers for HBV infection, specific HBV testing must be obtained. Hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) can be detected in the serum as well as high levels of IgM antibodies to the viral core antigen (IgM anti-HBc) during the acute phase [9]. An immune response targeted to clear the virus would clear the HBeAg and subsequently the HBsAg resulting in development of antibody to HBeAg and HBsAg with the appearance of antibodies to HBsAg indicating recovery from acute infection [10].

From acute infection, patients can go on to develop chronic hepatitis. Chronic HBV (CHB) infection is defined as presence of disease defined by HBsAg for at least 6 months. The risk of development of CHB infection is lowest in adults (<5%) and highest in neonates whose mothers are HBeAg positive (>90%) [11]. Most patients with CHB are asymptomatic unless they develop complications from their CHB either intrinsic to the liver or extrahepatic manifestations. History may not reveal a prior history of acute hepatitis given that acute episodes are often characterized by nonspecific symptoms and can be asymptomatic. Nonspecific symptoms of CHB may include fatigue or develop subacute symptoms of hepatitis. Evaluation should be directed at evaluating for signs and symptoms of cirrhosis, evaluation of alcohol intake and metabolic risks, family history of hepatocellular carcinoma (HCC), and HAV and HBV vaccination status.

There are five distinct phases of CHB infection including an immune tolerant phase, immune reactive HBeAg positive phase, inactive HBV carrier state, HBeAg-negative CHB, and occult CHB [12]. Laboratory findings associated with CHB infection is dependent upon the status of the chronic infection (see Table 2). Not all patients experience every phase, and the duration of phases can be variable; moreover, reversion or reactivation can occur between different phases without warning [12]. Family physicians must be comfortable interpreting HBV serologies (see Table 3) to determine the status of the disease not necessarily for the particular phase in the CHB disease process but more so for overall management and prevention of complications and spread of disease.

Management

The role of the family physician in the management of HBV, both acute and chronic, is correct

Table 2 Laboratory evaluation of phases of chronic HBV infection

	Immune tolerant	Immune reactant	Inactive HBY carrier	HBeAg-negative CHB	HBsAg negative
ALT	Normal	High	Normal	Normal or high	Normal
HBsAg	Positive	Positive	Positive	Positive	Negative
HBV DNA	High	High	Low or undetectable	High	Undetectable
HBeAg	Positive	Positive	Positive	Positive	Negative

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Table 3 Evaluating the HBY panel

Test	Result	Interpretation
HBsAg	Negative	Susceptible (no immunity)
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune (due to infection)
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune (due to vaccination)
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acute infection
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronic infection
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Four possible Interpretations[a]
Anti-HBc	Positive	
Anti-HBs	Negative	

Source: Immunization Action Coalition publication "Needle Tips," available at www.immunize.org

[a]Possible Interpretations

1. May be recovering from acute HBV infection
2. May be distantly immune and test is not sensitive enough to detect low level anti-HBs
3. May be susceptible with false-positive anti-HBc
4. May be chronically infected and have an undetectable level of HBsAg

identification and diagnosis of the disease as well as its status and severity. There is no specific treatment for acute HBV infection; however, with identification of CHB infection, family physicians must complete a thorough evaluation on patients with special emphasis on risk factors for complications (coinfection with hepatitis C virus or HIV, alcohol use, and family history of HBV infection and liver malignancy). Laboratory evaluation on the status of CHB infection including assessment of liver disease, markers for HBV replication (HBeAg, anti-HBe, HBV DNA), and tests for coinfection should be performed. While screening for hepatocellular carcinoma with alpha-fetoprotein levels and ultrasounds are recommended as part of the pretreatment and management algorithms, screening remains largely controversial [13]. A liver biopsy to determine the extent and severity of disease is no longer necessary in the process of deciding upon treatment. Individuals should also be vaccinated for hepatitis A.

The role of treatment is prevention of complications from CHB infection including cirrhosis, hepatic failure, and hepatocellular carcinoma. Goals that correlate with improvements in patient-oriented outcomes include HBV DNA suppression, HBeAg loss/seroconversion, ALT normalization, and HBsAg loss [12]. Current treatments include conventional interferon alpha, pegylated interferon alpha, and nucleoside/nucleotide analogues (NUCs), with pegylated interferon alfa-2a (Pegasys), entecavir (Baraclude), and tenofovir being first-line treatment options. Treatment regimens with specifications on criteria, drug regimen, and laboratory monitoring have been developed, most notably by the American Association for the Study of Liver Diseases (AASLD) [14] and the European Association for the Study of the Liver (EASL) [12].

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Prevention

Vaccination remains a significant mechanism of prevention of HBV infection. Vaccination is recommended for all children and adolescents, adults in certain ethnic groups, health care workers, and high-risk groups [15]. Postvaccination testing is recommended for individuals who may not elicit a complete response with anti-HBs performed 1–2 months following completion of the series. This should be performed in certain populations (persons on hemodialysis, persons who are immunocompromised, sex partners of persons positive for HBsAg, and health care personnel with revaccination indicated if the anti-HBs level is less than 10 mlU per mL) [15]. No more than two complete HBV vaccine series should be administered unless a patient is on dialysis where annual anti-HBs testing should be performed [15].

Routine screening for HBV infection is recommended for all pregnant women, which should be done through HBsAg at the first pregnancy visit. Screening is beneficial due to the significant benefit of postexposure prophylaxis in reducing the mother-to-child vertical transmission of HBV [15] accomplished through administration of HBV immune globulin and HBV vaccine to the infant within 12 h of birth. HBV is not an indication for a cesarean section as no current evidence suggests it to reduce transmission, and it is important to note that CHB infection is not a contraindication to breastfeeding.

Other screening can be performed on individuals at risk for HBV; however, routine universal screening is not recommended. Preventive strategies that also target these at-risk individuals that are part of a comprehensive public health strategy at risk reduction include screening of blood and blood products, needle exchange programs, and routine condom use. Postexposure prophylaxis is also available for health care workers and others exposed to bodily fluids from an individual with known or confirmed HBV infection.

Hepatitis C

Hepatitis C virus (HCV) is a single-stranded RNA virus transmitted through percutaneous exposure to infected blood and blood products as well as through sexual transmission; however, sexual transmission is less common. It can lead to both acute as well as chronic infections. HCV is likely responsible for the majority of hepatitis caused by what was formerly known as "non-A, non-B hepatitis" [16]. Risk factors for HCV infection include using IV or intranasal (IN) illicit drugs; HIV; recipients of blood transfusion, blood products, or organs before 1992; hemodialysis; sexual contact with those with HCV infection; piercings and tattoos; maternal-to-child transmission at birth; and sharing common household products such as razors or toothbrushes with someone infected with HCV.

Clinical Presentation and Diagnosis

In comparison to HBV and HAV infections, the acute phase of HCV hepatitis is much less likely to be symptomatic; if symptoms do develop, they are similar to the prodrome associated with HAV and HBV with nonspecific symptoms such as fatigue, nausea, anorexia, myalgias, arthralgias, weakness, and weight loss. Due to the largely asymptomatic presentation, it is unusual to perform diagnostic and laboratory evaluation unless an individual has a confirmed acute exposure. In this situation, a hepatitis viral load PCR test should be ordered to assess for possible transmission as antibody development is delayed.

HCV acute infection is much more likely than that of HBV infection to progress to a chronic infection. The definition of chronic HCV infection is the presence of virus for at least 6 months. Despite variations in data and studies, on average approximately 80% of individuals with acute HCV infection will progress to chronic infection, [17, 18] with 20% of those patients going on to develop cirrhosis (see Fig. 1) [18]. Therefore, it is clear that much more so than HBV, the chronic disease burden of liver disease secondary to HCV is significant. Symptoms of chronic HCV infection tend to be infrequent and again are nonspecific and typically mild, similar to that of acute infection. With acute infection being frequently asymptomatic, targeted history at risk factors is important in deciding to perform further

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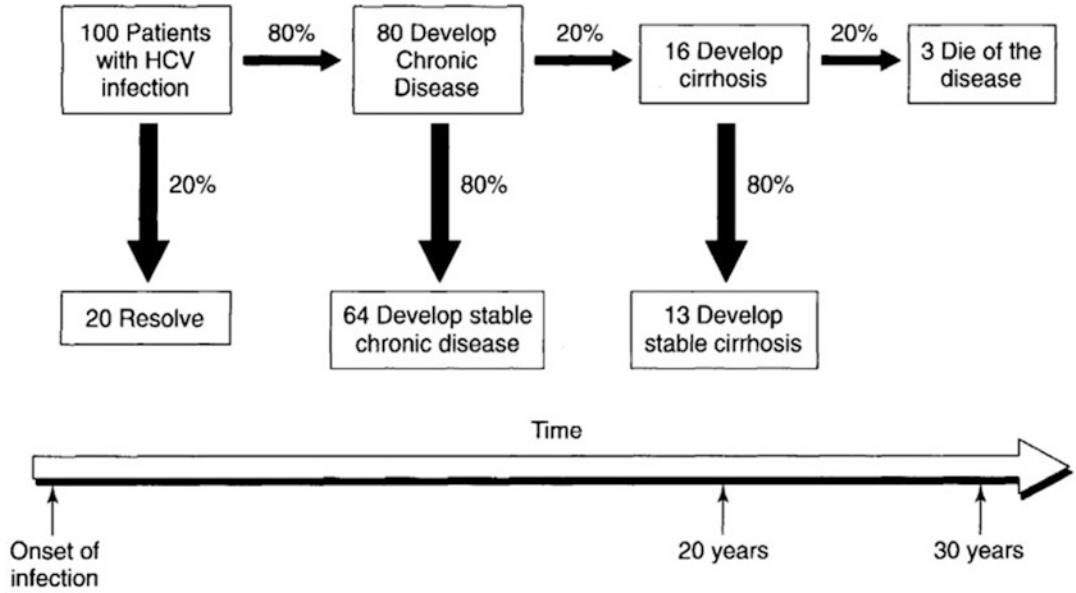


Fig. 1 The natural history of HCV infection is said to follow the "80/20 rule." While this is representative of population data, the percentages are approximate and vary based on several cofactors

clinical evaluation. Physical examination, similar to that of HBV, should be directed at evaluating for underlying signs of chronic liver disease or extrahepatic involvement with signs of cirrhosis and portal hypertension.

Laboratory evaluation with transaminases is not typically reliable to assist in the diagnosis of chronic HCV infection. The transaminases are typically normal and are only above 2 times that of normal in about 25% of patients and are rarely 10 times that of normal [19] and cannot be correlated with liver pathology. Formal diagnosis requires evaluation of the presence of antibody (HCAb) to HCV in the blood. Formerly, the initial test was an enzyme-linked immunoassay (ELISA) with the need for a recombinant immunoblot assay (RIBA) test performed for confirmation; however, newer third-generation ELISA testing enables a single antibody test with confirmation through further testing with a molecular assay that detect and/or quantify HCV RNA. The presence of HCV RNA for 6 months confirms chronic infection while a positive HCAb and negative HCV RNA suggests previous exposure to HCV with spontaneous clearance.

Management

Similar to HBV infection, the role of the family physician in the management of HCV is correct identification and diagnosis of chronic HCV infection. However, newer options for treatment facilitate this occurring in primary care with the CDC encouraging family physicians to treat HCV [20] with outcomes comparable to that of subspecialists [21]. Once diagnosed, patients should also be screened for HIV, as well as adequate immunity to HAV and HBV should be determined and provided if no immunity is apparent. In addition to making the diagnosis, the family physician should identify patients who qualify for treatment which includes assessment of fibrosis as the HCV viral load is not a sign of disease severity and fibrosis remains the most reliable prognostic factor to predict progression, morbidity, and mortality [22]. A number of methods are available to determine the degree of fibrosis with liver biopsy previously serving as the diagnostic standard; however, noninvasive tests using serum biomarkers or imaging such as serum fibrosis marker panels and transient elastography allow for accurate diagnosis of cirrhosis in most individuals [22, 23].

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The goal for HCV treatment is virological cure or sustained virological response (SVR), defined as the absence of detectable HCV RNA for at least 12 weeks. However, due to exposure, HCAb will remain positive for the patient's lifetime. SVR results in reduction of symptoms as well as both intrahepatic and extrahepatic complications of chronic HCV infection. While immediate therapy is reserved for patients with advanced fibrosis, compensated cirrhosis, liver transplant recipients, or severe extrahepatic complications, therapy should be considered earlier in the course given that SVR has significant benefits at reducing the overall complications. Treatments are determined based on the genotype and subtype of HCV infection as they have varying responses to different therapies. Genotype 1 is the most common form of chronic HCV seen in the United States and with previous drug therapies was known to be the most resistant to treatment.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) developed a guideline for the recommended treatments of chronic HCV infection directed at each individual genotype and subtype (found at http://www.hcvguidelines.org) [24]. Whereas most patients formerly received a regimen including interferon and ribavirin, recent years have brought newer antivirals to the scene including boceprevir (Victrelis) and telaprevir (Incivek) that reduced the use of interferon, yet side effects remained significant. Advancements and drug approvals led to even newer therapies, potentially removing the need for ribavirin use as well, including sofosbuvir/velpatasvir (Epclusa) and glecaprevir/pibrentasvir (Mavyret) for all genotypes, elbasvir/grazoprevir (Zepatier) for genotypes 1 and 4, and sofosbuvir/ledipasvir (Harvoni) for genotypes 1a, 1b, 4, 5, and 6. The AASLD and IDSA guideline is viewed as a living document during this time of significant advancements in the field of HCV treatment and also provides information on monitoring both prior to and after treatment.

Prevention

It is in large part due to the number of genotypes and subtypes of HCV that vaccine development against HCV has been difficult. Primary prevention should be targeted at reducing risk factors for transmission. Such strategies include screening of blood and blood products, needle exchange programs, and routine condom use. Education on these topics should not be reserved solely for those in contact with those infected with HCV but for all to ensure an appropriate public health strategy. Based on risk factors, individuals should be appropriately screened for HCV infection with an HCAb. This is recommended by the USPSTF as well as an additional recommendation that one-time screening for adults aged 18–79 [25].

Despite maternal-to-child transmission being the largest cause of HCV infection in children, routine testing of all pregnant women is not recommended. Additionally, inconclusive evidence remains on whether specific labor management strategies are effective at reducing transmission. Most practice involves limiting internal fetal monitoring, rupture of membranes, and instrumented deliveries. It is important to note that HCV infection is not a contraindication to breastfeeding. Newborns of mothers infected with HCV should be tested for HCV transmission; however, this is complicated by passage of maternal HCAb through the placenta. While diagnosis can be made earlier with two positive HCV RNA between 2 and 6 months of age in an infant, [26], the American Academy of Pediatrics (AAP) recommends testing with an HCAb at 18 months or later since HCV treatment is not recommended for infants less than 3 months [27].

Other Viral Agents

Hepatitis D and E are far less common viral hepatitides that have been demonstrated to cause infection. Hepatitis D virus, previously known as delta hepatitis, is an incomplete virus which is structurally an RNA virus that requires helper function of HBV to replicate and cause both an acute and chronic hepatitis. It is transmitted similarly to HBV and either occurs as coinfection or superinfection in an individual with chronic HBV. Hepatitis E virus is rare in the United States. It is similar to HAV such that it is transmitted via the

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fecal-oral route and only causes a self-limited acute infection. There are no vaccines or treatments currently available for hepatitis D or E viruses; however, hepatitis D can be prevented in an individual without HBV infection through the HBV vaccine.

Alcoholic Hepatitis

Alcoholic liver disease (ALD) is a serious health problem worldwide that encompasses several disease processes including alcoholic fatty liver disease (with or without steatohepatitis), alcoholic hepatitis, and cirrhosis. Excessive alcohol consumption can result in both short-term and long-term liver damage. Regular alcohol use, even for several days, results in fat deposition in the liver hepatocytes or steatosis (fatty liver). While abstinence reverses the process, steatosis places individuals who continue to drink at increased risk of progression to fibrosis and cirrhosis. Cirrhosis only develops, however, in a small number of patients with ALD [28]. While the mean intake of regular alcohol to result in liver disease is approximated to be around 100 g/day for more than 20 years, lesser amounts can potentially result in ALD as regular consumption of 30 g/day increases the risk for development of cirrhosis [29].

Clinical Presentation and Diagnosis

Given that excessive, regular alcohol consumption is necessary, most patients with ALD are often between 40 and 50 years old [30]. Careful history should be obtained from patients as they often will cease drinking with onset of symptoms due to disease severity. Excessive, regular alcohol consumption may not represent daily drinking as patterns of drinking can vary to include weekends or intermittent heavy drinking behaviors that family members are unaware. While long-term drinking (more than 20 years) is typically the overall course, individuals can present with ALD who have been drinking for shorter duration.

The individual will usually present with similar symptoms to that of viral hepatitis including fatigue, anorexia, jaundice, fever, right upper quadrant or epigastric pain, abdominal fullness, or bloating. Physical examination can demonstrate jaundice, icteric sclera, hepatomegaly, as well as possible findings of more chronic liver disease with cirrhosis including muscle wasting, ascites, or sequelae of portal hypertension. A bruit may be heard over the liver, a feature of more severe alcoholic hepatitis, has been demonstrated in over 50% with ALD [30]. While history can suggest that alcohol is the etiology for symptoms, one cannot completely rule out other causes of liver injury, and therefore, history and laboratory evaluation is needed to rule out other etiologies.

Laboratory findings associated with alcoholic hepatitis include transaminitis with AST-to-ALT ratio of 2:1 (levels are typically less than 300 IU/L and rarely higher than 500 IU/L), elevated serum bilirubin, elevated gamma-glutamyltransferase (GGT), and a leukocytosis with neutrophil predominance. Other laboratory findings can suggest severity of disease such as moderate to severe disease that would result in an elevated international normalized ratio (INR), anemia secondary to thiamine or folate deficiencies, low albumin and prealbumin in the setting of malnutrition, and thrombocytopenia from bone marrow suppression from alcohol or related to portal hypertension. Abdominal imaging (ultrasound, computed tomography, or magnetic resonance imaging) can also be utilized to assess for degree of steatosis, ascites, and cirrhosis. Liver biopsy is often helpful in assessing the severity of hepatocellular damage; however, it is not required for diagnosis.

Management

The overall management of alcoholic hepatitis for the family physician is targeted at patient education and safe cessation of alcohol. The potential complications due to alcohol use as well as a result of the alcoholic hepatitis such as ascites, hepatic encephalopathy, malnutrition, and alcohol withdrawal with or without delirium tremens should be treated as supportive care. Lifetime cessation of alcohol is critical to prevent the progression of disease, and patients should be supported through the process. Family physicians are poised to lead or be part of the multidisciplinary approach that

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may need to address comorbid alcohol use disorder (AUD). Relapse prevention medications can be utilized by family physicians. However, only baclofen has been studied in patients with alcoholic liver disease [31]. Acamprosate can be utilized as it is not metabolized by the liver; however, there are no studies regarding its efficacy for alcohol cessation in a population with alcoholic hepatitis.

While a number of therapies and treatments have been studied or suggested in the use of treatment of alcoholic hepatitis including psychotherapy, corticosteroids, pentoxifylline, infliximab, etanercept, nutritional support, oxandrolone, vitamin E, and silymarin (milk thistle extract), only corticosteroids have been shown to demonstrate improvements on mortality in specific populations with disease [32]. Liver transplantation may be necessary in severe cases; however, due to alcohol use being the etiology of their underlying disease process, patients often need to demonstrate sobriety for 6 months prior to consideration, and patients who might qualify for liver transplant may suffer significant complications during this time period.

Prevention

As ALD results from prolonged excessive alcohol intake, there is certainly a window of time for both screening and intervention to occur to combat alcohol misuse. The public health approach to the problem of alcohol use is screening, brief intervention, and referral to treatment (SBIRT). Family physicians play a critical role in screening individuals for alcohol use and misuse. The United States Preventive Services Task Force (USPSTF) recommends that "clinicians screen adults aged 18 or older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse" [33].

Drug-Induced Liver Disease

Due to its role in clearing and metabolizing chemicals, the liver is a particular target for damage from drugs. The cellular damage that occurs as part of drug-induced liver disease is typically a result of the drug or metabolite having a direct toxic effect on the liver or an immune-mediated response that causes liver injury. While liver damage from drugs and medications is common except in rare cases of drug-induced hepatitis, the majority of damage is reversible with cessation of the substance with a return to normal function [34]. One of the most frequent causes of hepatic injury due to a drug is from acetaminophen, which can be either acute or chronic use. It has been shown that over 1000 drugs have caused liver disease on more than one occasion [35] and therefore a comprehensive list is not easily developed. Table 4 lists some of the more common drugs that can induce liver damage.

HIV Liver Disease

Despite advancements in treatment that has made HIV infection a chronic illness, it remains a major global health issue. While HIV does not result in a direct injury or primary disease process in the liver, data demonstrates the burden of liver disease in patients with HIV is large, with liver disease being second only to AIDS-related complications in causing mortality [36]. Due to similarities in transmission routes, patients with HIV may also be coinfected with HBV and/or HCV. In fact, of liver-related deaths in patients with HIV, 66% were secondary to complications of HCV and 17% secondary to complications of HBV [36]. This is largely secondary to fibrosis and complication rates in patients coinfected with HIV and either HBV or HCV being much higher [37]. Patients with HIV are also at risk of developing opportunistic infections that may also cause liver damage including mycobacterium tuberculosis (Tb), mycobacterium avium complex (MAC), and cytomegalovirus (CMV).

In addition to infectious etiologies, increasing recognition of highly active antiretroviral therapy (HAART) as a source of liver damage

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Table 4 Common potential hepatotoxic medication agents

Over the counter (OTC) agents	Acetaminophen (Tylenol)
	NSAIDs (ibuprofen, naproxen, etc.)
Anti-arrhythmics	Amiodarone
	Diltiazem
Antibiotics	Isoniazid
	Nitrofurantoin
	Amoxicillin/clavulonic acid
	Rifampin
	Tetracycline (minocycline, tetracycline)
Antiepileptics	Phenytoin
	Carbamazepine
	Valproic acid
Antifungals	Azoles (ketonazole, fluconazole)
	Amphoteracin
	Terbinafine (systemic)
Anti-hyperglycemics	Sulfonylureas (glipizide, glyburide)
	Thiazolidinediones (pioglitazone)
Anti-hyperlipidemics	Statins (rosuvastatin, simvastatin, etc.)
	Nicotinic acid (niacin)
	Fibrates (gemfibrozole, fenofibrate)
Endocrinologic agents	Methimazole
Hormonal agents	Anabolic steroids
	Estrogen and oral contraceptives
	Testosterone
Rheumatolic agents	Methotrexate
	Quinadine
Psychiatric agents	Atypical antipsychotics (quetiapine, etc.)
	Nefazodone
	Trazodone
	Venlafaxine

Table 5 Risks of HAART on liver disease

NRTIs	
Caution	Didanosine (ddl)
	Stavudine (d4T)
	Zidovudine (ZDV/AZT)
	Zalcitabine (ddC)
Safer	Abacavir (ABC)
	Tenofovir (TDF)
	Lamivudine (3TC)
	Emtricitabine (FTC)
Integrate inhibitors	
Safer	Raltegravir (RAL)
	Elvitagravir (EVG)
	Dolutegravir (DTG)
Entry inhibitors	
	Maraviroc (MVC)
	Enfuvirtide (INN;T20)
NNRTIs	
Caution	Nevirapine (NVP)
	Efavirenz (EFV)
Safer	Etravirine (ETV)
	Rilphirine (RPV)
Protease inhibitors (Pi's)	
Caution	Ritonavir (RTV)
	Telapravir (TPV)
Safer	Indinavir (IDV)
	Atazanavir (ATAZ)
	Saquinavir (SQV)
	Lopinavir (LPV)
	Darunavir (DRV)
	Amprenavir (APV)
	Nelfinavir (NFV)
Enhancer	
Safer	Cobicistat (COBI)

is also occurring. Monitoring transaminases is recommended for newly diagnosed and newly treated patients as HIV infection with high viremia alone may result in transaminase elevation with reduction as HAART is initiated [38]. Additionally, many patients with HIV whose liver enzymes are elevated are asymptomatic during this time [39]. Due to combination therapies, it can be difficult to determine the culprit drug resulting in liver damage. Table 5 lists drugs from HAART regimens with documented liver toxicity [40].

Patients with HIV should also be appropriately screened for other potential etiologies of liver disease including alcohol-induced disease, drug-induced liver disease, and nonalcoholic fatty liver disease (NAFLD). NAFLD is the hepatic manifestation of metabolic syndrome and is noted to have

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significantly higher rates in those infected with HIV compared to the general population [41].

Hepatocellular Carcinoma

Despite most malignancy involving the liver being due to metastatic disease commonly from colorectal cancer, hepatocellular carcinoma (HCC) remains a significant cause of morbidity and mortality worldwide. Most of the disease burden remains in developing countries where HBV infection is endemic; however, HCC secondary to HCV infection is a significant cause of cancer-related death in the United States [42], with the incidence tripling and the 5-year survival rate remaining below 12% [43]. While significant risk factors are largely infection with HBV or HCV, preexisting cirrhosis is found in more than 80% of individuals diagnosed with HCC [44]. Therefore, any etiology that would result in chronic liver injury resulting in cirrhosis should be considered a risk factor for HCC. HCC is rarely seen in individuals younger than 40 years of age, and peak incidence occurs around age 70 with a predilection for males as the rates are two to four times higher in males than females [45].

Clinical Presentation and Diagnosis

Given that a large majority of patients with HCC have underlying cirrhosis, the presentation of HCC is almost indistinguishable other than typical signs of cirrhosis including fatigue, upper abdominal pain, weight loss, early satiety, encephalopathy, and potentially jaundice. HCC can be suspected in a patient who develops acute decompensated cirrhosis who has previously been stable. Solid liver lesions are often noted with screening in patients at risk for HCC through ultrasound screening, which according to the AASLD should be performed in high-risk patients every 6 months [46]. As previously noted, it is increasingly recognized that alpha-fetoprotein lacks adequate sensitivity and specificity to be utilized as a screening or diagnostic aid [47]. Ultrasound findings are monitored based on their size with testing and diagnosis becoming increasingly possible with the use of noninvasive imaging techniques. Biopsy, although reassuring, cannot completely rule out the presence of HCC, and lesions, despite normal biopsy, need to be followed until disappearance or progression to malignant disease [48].

Management

Based on the staging at diagnosis (Barcelona Clinic Liver Cancer (BCLC) staging system) [49], there are several potentially curative or palliative approaches to treatment [50] including resection, radiofrequency ablation, chemoembolization, medication therapy, and liver transplantation. While family physicians should be aware of the potential treatment options for HCC and remain supportive in the care, treatment of HCC is typically performed in conjunction with hepatologist or gastroenterologist management.

Prevention

Prevention of HCC is targeted at modification of the underlying risk factors for HCC. HBV vaccination remains an effective prevention strategy for avoiding HBV viral infection and resultant cirrhosis. Primary prevention seems to be the most effective strategy at prevention. While treatment of HBV infection and HCV infection does reduce the risk of development of HCC, it does not completely eliminate this risk.

Family Issues of Diseases of the Liver

The family physician is challenged with being on the front lines of prevention, patient education, risk factor assessment, diagnosis, management, and monitoring of patients and families afflicted with liver diseases. Advances in treatment have expanded the role of family physicians in addressing diseases of the liver. As many common medications can cause liver damage, family physicians must be aware of the pharmacological properties of the medications they are prescribing and use caution in patients to avoid drug-drug interactions as well as use safe medications in

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patients with liver disease. Additionally, as family physicians care for patients across the age spectrum, diagnosis of viral hepatitides as well as appropriate testing and treatment targeting at reducing maternal-to-child transmission is important information for the practicing family physician. While the family physician has a duty to respect the privacy of the patient with regard to possible diagnosis of HBV and HCV chronic infections, he also cares for their family members and has the unique role to protect privacy but also protect his patients from transmission. Furthermore, as alcohol-related disorders cause not only physical damage but also rifts in relationships and connections with family and friends, the family physician has a critical role in coordinating care as well as a comprehensive addiction treatment program including patient and family. Poised with an effective role in public health, family physicians ensure appropriate education and counseling occurs for patients and family members on risk reduction as well as discussion of typical course and prognosis for chronic liver diseases. While the complications of chronic liver disease are often managed by a multidisciplinary team, the intrinsic value of the family physician in this process due to the above cannot be understated.

Conclusion

Diseases of the liver represent a variety of conditions that vary in chronicity, complications, and management strategies. With viral hepatitides, alcoholic liver disease, and drug-induced liver disease being some of the most common forms of both acute and chronic liver disease, the family physician plays a critical role in the diagnosis and management. Due to the significant family issues associated with liver disease and the family physician's role in diagnosis and management, it is critical that the practicing family physician have an awareness of the diagnosis, management, and prevention strategies and approach them with an evidence-based perspective.

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Diseases of the Rectum and Anus

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Anatomy of the Rectum and Anal Canal

The rectum extends from the rectosigmoid to the anorectal junction (about 15 cm); the anal canal measures about 5 cm, extending from the lower border of the anal crypts at the dentate line to the anal verge [1]. The rectum and the anal canal above the undulating dentate line are lined by columnar epithelium and below by stratified squamous epithelium that transitions to the skin at the anal verge [1]. Innervation above the dentate line is sympathetic (L-1 to L-3) and insensate; below is somatic (pudendal nerves, S2–S4) [1]. The vascular supply of the anorectal region is through the superior, middle, and inferior hemorrhoidal vessels.

Hemorrhoids followed by anal fissures, anorectal abscesses and fistulas, fecal incontinence, rectal prolapse, pruritus ani, proctitis, hidradenitis suppurativa, condyloma acuminatum, and anorectal cancer are common problems pertaining to the anorectal region.

Hemorrhoids

Background

Hemorrhoids represent the enlarged normally observed fibrovascular cushions (hemorrhoidal cushions) lining the anal canal [2]. Hemorrhoidal cushions help exercise bowel control by sustaining a resting pressure; vascular engorgement associated with increasing intra-abdominal pressure (as in laughing, coughing, sneezing) closes the anal canal, helping maintain continence. The innervation feedback from the hemorrhoidal cushions helps differentiate between flatus, liquid, and solid stool [2]. Aging and continual straining associated with constipation cause degeneration and weakening of the securing fibrous tissue, detachment of the cushions from the internal sphincter, and prolapse. The overlying mucosa also becomes loose, bulges into the anal canal, and becomes thin and friable due to sustained trauma by feces and ulcerates, sometimes causing bright red rectal bleeding.

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Epidemiology

Hemorrhoids are most common among men and women between 45 and 65 years of age with hemorrhoid-related symptoms being experienced by nearly one in two Americans over 50 [3]. Predisposing factors include older age, irregular bowel habits, decreased fiber intake, obesity, pregnancy, ascites, positive family history, and absent valves within the hemorrhoidal veins. Hepatic cirrhosis, portal hypertension, and portal vein thrombosis also predispose to development of hemorrhoids.

Classification

Hemorrhoids may be located above (internal) or below the dentate line (external) or both above and below (intero-external) [4, 5]. Based on symptoms of bleeding and prolapse, hemorrhoids are classified as grade 1 or first degree (bleeding with prominent hemorrhoidal veins, without mucosal prolapse), grade 2 or second degree (bleeding and mucosal prolapse on straining reducing spontaneously), grade 3 or third degree (bleeding and mucosal prolapse on straining, requiring manual reduction), and grade 4 or fourth degree, representing persistent prolapsed hemorrhoids with or without complications (strangulation, ulceration, fibrosis, gangrene, sepsis) [4–6].

Diagnosis

History

Patients with hemorrhoids experience painless bright red bleeding during or after stooling. Constipation and straining may be present. With second-degree or more advanced hemorrhoids, mucus discharge, a sense of incomplete defecation, pruritus ani, and a perianal rash are noticed. Thrombosis or ulceration leads to perianal pain and swelling, bleeding, and a bloodstained discharge [7]. Blood from more proximal sources (polyps, diverticula, angiodysplasia, ischemic colitis) is usually darker or clotted blood mixed with stool. Fever, throbbing pain, redness, swelling, and inability to sit indicate perianal sepsis. Abdominal discomfort and distention, anorexia, weight loss, and worsening constipation or persisting diarrhea should suggest cancer, ischemic colitis, or inflammatory bowel disease (IBD).

Examination, Special Testing

Physical examination usually yields little information in healthy patients. Presence of anemia indicates a different pathology. Jaundice, hepatosplenomegaly, and enlarged abdominal wall collaterals characterize hepatic cirrhosis and portal hypertension. A palpable abdominal mass suggests possible colon cancer and, if tender, a peridiverticular mass. Perianal inspection, digital rectal examination (DRE), and anoscopy in the left lateral (Sims') or the knee chest position complete the initial patient assessment. Perianal inspection may reveal skin tags, prolapsed and thrombosed hemorrhoids, anal fissure or abscess, excoriation, fistula, cancer, or condyloma. Bearing down during DRE or anoscopy relaxes the sphincter and causes second- and third-degree hemorrhoids to prolapse. Uncomplicated hemorrhoids are impalpable and non-tender; when thrombosed or fibrosed, hemorrhoids are palpable; and prolapsed and strangulated hemorrhoids are tender. Insertion of a side-viewing anoscope causes hemorrhoids to bulge into the lumen. When examining a patient in the Sims' position, the anal cushions (internal hemorrhoids) are usually located at the 11 o'clock (left anterior), 3 o'clock (right lateral), and 7 o'clock (left posterior) positions. Prolapsed hemorrhoids should be reduced to minimize risk of strangulation and ulceration. Patients over 50 years with rectal bleeding should undergo a colonoscopy, even though hemorrhoids are detected [4, 5, 6].

Treatment: Non-operative

Adequate fluid and fiber intake (20–35 G daily) is the primary first-line non-operative therapy for patients with symptomatic hemorrhoids of all grades [4, 5]. Many symptoms associated with

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hemorrhoids (bleeding, prolapse, and pain) improve on increasing fiber intake. Sitz baths (a warm water bath in which the patient squats or sits), analgesics, and anti-inflammatory medications relieve pain and decrease tissue edema and sphincter spasm in patients with thrombosed hemorrhoids and following hemorrhoidectomy [8]. Oral flavonoids and topical preparations such as Preparation H, glyceryl trinitrate 0.2% ointment applied three times daily for 14 days, and nifedipine 0.3% with lidocaine 1.5% ointment applied twice daily for 14 days also decrease symptoms associated with hemorrhoids and their complications [9, 10]. Exercising and losing excess weight are also beneficial.

Office Procedures

The rubber band ligation (RBL) technique is useful in treating grade I through III internal hemorrhoids. A small rubber band is loaded onto a hollow applicator, the hemorrhoid is grasped 1 cm or more above the dentate line and pulled inside the applicator, and the rubber band is released at the base of the hemorrhoid, which sloughs off over 5–7 days. Moderate pain can follow RBL. One or more hemorrhoids can be banded at the same or subsequent office visits [5]. RBL is successful in most (93%) patients with grade II and III hemorrhoids, though 11% symptomatic recurrence is observed over 2 years [11]. Suction ligation, in which an anoscope/ligator is attached to the wall suction (vacuum suction ligation), is associated with less bleeding and post-procedure pain. Complications following RBL are rare (<1%) and include band placement at or near the dentate line (requires removal and reapplication), urinary retention, rectal bleeding (post-procedure or 7–10 days later, usually self-limiting), extrusion of the band, pain, ulceration, thrombosis, and perineal infection [3].

Sclerotherapy involves injection of an irritant (5 ml sodium morrhuate, 5% phenol in oil, hypertonic saline) through the anoscope into the submucosa at the apex of the hemorrhoid, causing ischemia and fibrosis, fixing the hemorrhoid to the rectal wall, decreasing bleeding and prolapse. Though effective in grade I, II, and III hemorrhoids, the majority of patients over time experience recurrence, especially in grade III hemorrhoids [12]. Complications include mucosal sloughing, thrombosis, abscess formation, and bacteremia. Sclerotherapy using Polidocanol 2% with or without foam is efficacious in I, II, and III hemorrhoids with improvement observed in most cases [13].

Infrared photocoagulation (direct application of infrared waves through the anoscope) produces superficial tissue destruction, reducing blood flow and tethering the hemorrhoid to the underlying tissues. It is most useful in grade I and II hemorrhoids [5].

In-Hospital Surgery

Hemorrhoidectomy is indicated in patients with intero-external hemorrhoids and grade III and IV hemorrhoids, in hemorrhoids recurring after office procedures, or in patients intolerant of office procedures [5]. The surgery, performed under general or regional anesthesia, requires distal bowel preparation to minimize soiling during and after the procedure. Preoperative antibiotic administration is unnecessary. In open hemorrhoidectomy, the hemorrhoid is excised after ligating the pedicle, and the raw area is allowed to granulate. In closed hemorrhoidectomy, the raw area is closed primarily. The LigaSure procedure involves sealing of the hemorrhoidal tissue between the LigaSure forceps during dissection, minimizing tissue destruction, blood loss, and post-procedure pain [14]. Using an ultrasonic scalpel for dissection is an advance found to result in less post-procedure pain and complications and earlier return to work [5]. Bleeding, urinary retention, wound infection, fecal incontinence, and anal stricture may follow surgery (all uncommon). In the "stapled hemorrhoidopexy" (hemorrhoidectomy), a ring of anal mucosa with the underlying fibrovascular cushions is removed using a modified, circular anastomotic stapler. Though bleeding, wound complications, constipation, and pruritus are decreased, recurrence rates and prolapse are higher than in conventional hemorrhoidectomy [15]. The Doppler-guided trans-anal hemorrhoidal ligation involves suture ligation of the hemorrhoidal vessels after localizing them with Doppler ultrasound. This procedure, best applicable to grade II and III hemorrhoids, allows most patients to be

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discharged at 24 h and return to work in 2–3 days. Complication rates are low, though pooled recurrence rates of 17.5% were observed, higher in grade IV hemorrhoids [16].

External Hemorrhoids

Most patients with thrombosed external hemorrhoids (perianal hematoma) improve with sitz baths twice daily, stool softeners, and analgesics. Patients presenting within 72 h of onset of symptoms benefit from evacuation of the clot [5]. This is usually performed under local anesthesia using lidocaine (1–2%). Following clot clearance, bleeding from the base and edges is managed with sutures, packing, or electrocautery, and analgesics, stool softeners, and sitz baths are continued until healing is complete. Perianal skin tags may cause irritation or interfere with hygiene but rarely require excision.

Prolapsed and strangulated hemorrhoids are best managed with stool softeners, analgesics, rest, warm soaks, and ice packs to decrease pain and swelling, minimizing constipation and tissue ischemia. Swelling and pain resolve over several days; the residual hemorrhoid may then be managed by RBL or hemorrhoidectomy. Immediate excision leads to excess tissue removal, anal canal narrowing, and infection. Spreading perianal infection and tissue necrosis occur occasionally, requiring immediate debridement and broad-spectrum antibiotics [3].

Nonhemorrhoidal Anorectal Diseases

Anal Fissure

Epidemiology and Classification

Anal fissures are painful linear cracks in the anal mucosa distal to the dentate line. They may be acute (<8 weeks) or chronic (symptoms persisting >8 weeks) [17]. Anal fissures are more common in younger adults and have an equal sex distribution. The majority (>90% in men; 75% in women) are posterior; anterior fissures have a female preponderance. Lateral or multiple fissures may follow trauma, infections (syphilis, tuberculosis, anorectal abscesses, herpes, or human immunodeficiency virus – HIV – infection), cancer, and IBD [17, 18]. Low fiber intake, chronic diarrhea or constipation, excessive laxative use, and anal trauma (including surgery) also predispose to anal fissures [18]. Fiber increases stool volume and bulk minimizing anorectal trauma during defecation. Anal surgery predisposes to tissue ischemia through fibrosis, increasing the risk of non-healing fissures.

Diagnosis

Diagnosis is clinical. Severe pain initiated by and persisting for several hours after defecation is characteristic of acute fissures [17]. Bright red blood is often seen in the toilet paper, stool, or toilet bowl. Constipation (due to painful evacuation and unwillingness to defecate), perianal discharge, pruritus, and a perianal mass may also be present.

Acute fissures usually appear as midline tears, with a skin tag extending distally from the base of the tear (the "sentinel pile"). There is significant perianal spasm; DRE or anoscopy is painful. Chronic fissures are less painful and tender and evidence more scarring and raised edges, the floor exposing the white horizontal fibers of the internal sphincter.

Perianal tenderness and induration or lateral, multiple, or recurrent fissures should prompt a search for a more definitive cause. Dark-field microscopy of perianal discharge may demonstrate spirochetes. Serum antibody testing may detect treponemal or HIV antibodies. Imaging studies (endoanal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI)) are useful in revealing the extent of anal involvement and perianal/extra-anal extension of infection or malignancy. Endoscopy is valuable in detecting proximal bowel pathology (IBD, malignancy) associated with chronic or multiple fissures; biopsies confirm IBD or cancer.

Treatment

Non-operative treatment measures improve pain and bleeding, heal fissures in nearly 50% of patients, and are advocated initially in both acute and chronic fissures [17]. These include fiber

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Table 1 Treatment options in acute and chronic anal fissures (text from multiple sources)

[a]Nonsurgical measures – in acute and chronic fissures	
Dietary fiber/fiber supplements	Increase dietary fiber to 20G–35G daily Fiber supplements (psyllium, Citrucel, FiberCon) Increase intake gradually over 6 weeks. Bloating a side effect
Sitz baths	Patient sits in a shallow tub of warm water, to which some salt is added, for 15–20 min. Relieves pain and itching, relaxes perianal spasm, removes discharge, and assists with healing of raw areas
Medicated gels/ointments (all applied twice daily for 6–8 weeks)	Nitroglycerin 0.2–0.4% ointment Diltiazem gel or ointment 2% Nifedipine 0.3% with lidocaine 1.5% ointment Relieves pain and spasm and assists with healing
Botulinum toxin	Twenty units injected into the internal sphincter muscle on both sides. Relieves pain and spasm and assists healing
Surgical measures – In acute fissures not responding to non-operative measures and in chronic fissures	
Lateral internal sphincterotomy (LIS)	Full thickness of internal sphincter divided distal to the dentate line away from fissure (usually lateral). Relieves spasm and assists healing
Tailored LIS	Sphincterotomy stops at the apex of the fissure. Relieves spasm and lessens risk of incontinence compared to LIS
Subcutaneous fissurotomy, anal advancement flap	In patients with preexisting continence problems or in those with normal sphincter tone (postpartum women) Sphincter not divided Less risk of postoperative incontinence

[a]Usually continued for 6 weeks

supplementation, bulk laxatives, sitz baths, topical corticosteroid, local anesthetic, or medicated creams (nitroglycerin ointment, diltiazem gel, and nifedipine with lidocaine ointment) (Table 1). They relieve constipation and minimize sphincter spasm and pain, hastening healing, and should probably be continued for 6 weeks in acute fissures before surgery is considered. Injecting botulinum toxin (Botox) relaxes the internal sphincter hastening cure. Topical nifedipine with Botox injection induces lasting healing in chronic fissures [19]. Surgery is, however, consistently superior to medical therapy in chronic fissures and may be offered without initial conservative treatment failure [17].

Lateral internal sphincterotomy (open or closed) is the recommended surgical treatment for acute anal fissures not responding to conservative treatment and in chronic fissures (Table 1) [17]. The internal sphincter muscle distal to the dentate line is incised laterally (as most fissures are anteroposterior), decreasing sphincter pressure and promoting healing. The upper third of the sphincter and the anal mucosa remains intact, maintaining continence. The sentinel pile may be resected at the same sitting. Sphincterotomy relieves pain (95%) and results in healing in most (93.3%) patients with chronic fissures [20]. Resulting incontinence to flatus and liquid stool is potentially minimized by halting the sphincterotomy at the apex of the fissure (tailored sphincterotomy) rather than extending it to the dentate line [17]. Patients with preexisting continence problems or normal sphincter tone may benefit from techniques that preserve the internal anal sphincter (anal advancement flap and subcutaneous fissurotomy). Combining sphincterotomy or anal advancement flap with Botox injection decreases post-procedure pain, enhances healing, and minimizes fecal incontinence [17].

Anorectal Abscess

Pathogenesis and Classification

Anorectal abscesses originate from cryptoglandular infections at the dentate line (occluded anal gland duct with superimposed bacterial overgrowth and suppuration) [21, 22]. Anorectal abscesses may be perianal, ischiorectal, intersphincteric, or supralevator. A perianal

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abscess (most common) is a collection of pus in the perianal tissues. The abscess may extend into the ischiorectal fossa (ischiorectal abscess – unilateral or bilateral), forming a horseshoe-shaped collection, or, more rarely, tracks upwards between the sphincters (intersphincteric) and through the levator ani musculature (supralevator). The infection is generally polymicrobial, involving both gram-negative organisms and anaerobes, indigenous to the gut.

Diagnosis

Patients with perianal abscess present with perianal swelling and throbbing pain, aggravated by pressure and defecation. Systemic symptoms (fever, chills, vomiting, and diaphoresis) characterizing sepsis are generally absent. Ischiorectal and higher-level suppurations often result in dull throbbing perianal or pelvic pain, low back or buttock pain, and systemic symptoms [22, 23]. Physical examination reveals a brawny red, extremely tender, indurated perianal mass. DRE is extremely uncomfortable but might reveal induration extending along the lateral anorectal wall in an intersphincteric or ischiorectal abscess. Supralevator abscesses usually have few local physical findings. Associated anal fistulas may be observed in over half of patients (30–70%) [22].

Treatment

Incision and drainage (under local anesthesia with or without conscious sedation) is the treatment of choice in perianal abscess [21, *22*]. The incision is deepened to enter the abscess cavity; any slough is removed, the cavity is irrigated with saline and a drain left in, or the cavity is packed loosely; the raw area heals by secondary intention. Antibiotics, unnecessary in uncomplicated perianal infections, do not decrease recurrences or healing times [21, 22]. Antibiotics effective against both aerobes and anaerobes are a consideration in diabetics, in those immunosuppressed, in those with extensive perianal cellulitis or prosthetic devices, and in those with systemic sepsis. Over a third of patients may have recurrent perianal infection or a fistula following drainage, more frequent in those under 40 years of age [24]. Patients with ischiorectal or intersphincteric abscesses may require a more formal drainage procedure under general anesthesia; any associated fistulous tract is laid open at the time of abscess drainage, or a seton (suture, rubber band, Silastic vessel loop) is left in the fistulous tract, and the abscess cavity is allowed to heal. Internal sphincterotomy is useful in draining intersphincteric abscesses into the anal canal. Concomitant simple fistulas may be laid at the time of abscess drainage.

The diagnosis of supralevator (pelvic) abscess usually requires initial confirmation by imaging (US or CT) to delineate its extent and determine the underlying cause (IBD, appendicitis, cancer) [25]. These patients usually require a combination of broad-spectrum antibiotics, imaging-assisted drainage, and treatment of the underlying cause. A temporary colostomy for fecal diversion may be necessary to enable resolution of distal (anorectal) infection.

Anorectal Fistula

Pathogenesis and Classification

Anorectal fistula (fistula-in-ano) is an abnormal tract connecting the anorectum to the perianal skin lined with granulation tissue and producing a mucopurulent or feculent perianal discharge. Most follow cryptoglandular infection and spontaneous rupture or drainage of a perianal abscess and denote continued perianal infection and/or formation of an epithelialized tract [22]. Anorectal fistulas may also complicate IBD, radiation, cancer, actinomycosis, lymphogranuloma venereum (LGV), tuberculosis, trauma including obstetrical injuries, and foreign body. It is twice as common in adult males; among infants it is seen solely in boys.

Anorectal fistulas are classified into intersphincteric (type 1, fistulous tract in the intersphincteric plane, most common, 45%), transsphincteric (type 2, tract passing from the anal canal through the external sphincter to the ischiorectal fossa, 30%), suprasphincteric (type 3, tract passing

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from the anal canal along the intersphincteric plane and over the puborectalis muscle into the ischiorectal fossa, 20%), and extrasphincteric (type 4, tract outside the sphincter complex passing through the ischiorectal fat and levator ani muscles connecting the rectum and the skin, least common, 5%) [26]. Fistulas may also be designated as simple (most common, usually intersphincteric and low transsphincteric fistulas) or complex (high transsphincteric, extrasphincteric, or suprasphincteric fistulas) based on the risk of fecal incontinence following surgery. Anterior fistulas in women and fistulas associated with IBD (Crohn's disease) and cancer or following radiation are also considered complex [27].

Diagnosis

Symptoms include perianal pain and swelling followed by purulent or bloodstained perianal drainage and dyschezia. Passing bowel contents through the perianal opening indicates a high (rectal) internal opening. History of abscess drainage (in 50% of patients), other anorectal surgery, radiation, or pelvic trauma may be present. Perianal examination and DRE may reveal redness, swelling, induration, fluctuance, and external openings of fistulas with drainage or granulations. "Goodsall's rule" states that all fistulous tracts posterior to a line, drawn between the ischial spines with external openings within 3 cm of the anal margin, have a curvilinear course to the posterior midline of the anal canal. Tracks with anterior external openings originate from the nearest crypt and have a straight course to the anal canal.

Proctosigmoidoscopy is useful in visualizing the internal opening(s) and may show other mucosal abnormalities such as proctitis [27]. Imaging studies (endoanal ultrasound, CT, MRI) are useful in defining anatomy and guiding management in patients with complex fistulas.

Treatment

The goal of treatment is to obliterate the fistulous tract and openings while causing negligible sphincter disruption and maintaining continence. Treatment is determined by the etiology and anatomy of the fistula, degree of symptoms, and patient comorbidities [27]. Asymptomatic fistulas associated with Crohn's disease do not need treatment. Fistulotomy (fistulous tract laid open and allowed to heal) is highly successful, maintains continence, and is recommended for simple perianal fistulas, including Crohn's fistulas; marsupialization (suturing mucocutaneous edges) may further enhance wound healing [22, 27]. Coexisting abscesses are drained. Complex or recurrent fistulas, prior surgery, female sex, preexisting incontinence, and Crohn's disease increase risk of persisting or recurrent infection and postsurgical incontinence. Ligation of the intersphincteric tract (LIFT procedure) is an effective treatment option in simple and complex transsphincteric fistulas with little morbidity and high success [22]. Fistulectomy (complete excision of the tract and surrounding tissue in one block) results in larger tissue defects, requires longer healing times, and produces more incontinence while not improving recurrence rates. Anal fistulas in infants and children respond well to abscess drainage and antibiotics; immediate fistulotomy is avoided.

Debridement of the fistulous tract and injection of fibrin glue is an option in both simple and complex anal fistulas, especially in patients at risk for incontinence [22, 27]. A bioprosthetic anal fistula plug closing the internal opening, endoanal advancement flaps, and passing a seton (suture, rubber band, Silastic vessel loop) through the fistula tract to initiate a foreign body reaction and scarring are other options in treating complex fistulas. The seton is gradually tightened to cut through the fistula; fibrosis maintains sphincter integrity. Both fibrin glue and the fistula plug have been found to be relatively ineffective in recent studies with healing rates under 50% [22].

Perianal involvement including fistulas may be seen in over half of patients with Crohn's disease. Medical measures result in healing in many patients [27]. Surgical approaches, though less effective with higher recurrence rates, are useful. Permanent fecal diversion or proctectomy is rarely required for severe persisting disease [27].

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Initial non-operative treatment of rectovaginal fistulas following obstetric injuries for 3–6 months (treating infection, wound care) promotes healing in over half of patients [22]. Using a seton results in symptomatic relief and encourages resolution of infection. Endorectal advancement flap with or without sphincteroplasty is optimal for most simple rectovaginal fistulas. More complex or high rectovaginal fistulas associated with fecal incontinence may require extensive excisional and reconstructive procedures (episioproctotomy, proctectomy with coloanal anastomosis, gracilis or bulbocavernosus muscle flap reconstruction).

Anal Incontinence

Background

Anal incontinence is the inability to control the evacuation of bowel contents (flatus or feces) or recurrent uncontrolled passage of fecal material [28]. It is frequently seen among the elderly (over 65) and approaches 50% among nursing home residents, many of whom are also incontinent of urine. Fecal incontinence is twice as common among Caucasian as in African-American women. Functional limitations, hypertension, neurological disorders, obesity, physical inactivity, pregnancy, smoking, and type 2 diabetes mellitus also increase its prevalence [29]. Fecal incontinence may also follow anatomical or physiological changes resulting from trauma, surgery or disease, changes in stool characteristics, cognitive deficits, malabsorption, medications, or underlying psychiatric conditions (Table 2) [28]. Congenital anomalies, developmental disorders, encopresis (fecal retention), and mental retardation are the predominant causes among children [28]. Incontinence causes significant limitations in social interactions and loss of self-esteem and increases health-care costs.

Diagnosis

A problem-specific history should be obtained [28, 30]. Examination should address the patient's general well-being with particular focus on neurological disorders and deficits and abdominal and anorectal pathology. Generalized weakness, balance and gait disturbances, and need for ambulatory aids imply functional incontinence. A speculum and a digital rectovaginal examination may detect perineal and anal hypotonia and intrarectal pathology. Contracting the perianal muscles over the palpating digit also helps assess pelvic floor integrity. Pelvic organ prolapse is best evaluated by asking the squatting patient to strain (Valsalva). Proctosigmoidoscopy detects rectal ulcers associated with prolapse, IBD, and neoplasms. Colonoscopy is recommended in patients $\geq$50 years.

Imaging and physiologic studies complement clinical evaluation. Endoanal ultrasound (EUS) identifies sphincter defects in suspected sphincter injury. Anal manometry evaluates maximum resting and squeeze pressures in the anal canal, the rectoanal inhibitory reflex, and the rectal sensation and compliance. Most patients with fecal incontinence have manometric abnormalities. Electromyography (EMG) identifies injury to the sphincter muscles. Pudendal nerve terminal motor latency (PNTML) measures intactness of the pudendal nerve-anal sphincter neuromuscular unit; PNTML abnormalities correlate well with poor surgical outcomes. Scoring systems incorporating the patient's subjective experience of fecal incontinence as well as its effect on quality of life help select patient for treatment and evaluate treatment results [30].

Treatment

Goals of treatment are to reestablish normal evacuation, improve lifestyle, and restore functional capacity. Conservative measures improve continence, quality of life, psychological well-being, anal sphincter function, and patient coping strategies. Mucocutaneous and soft tissue complications (skin excoriations, decubitus ulcers, abscesses) should be handled through judicious drainage, antibiotics, antifungals and barrier creams, or, in extreme cases, temporary or permanent fecal diversion until healing is complete.

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Table 2 Common causes and mechanisms of fecal incontinence (Modified from text in Ref. [28])

Enumeration of causes	Mechanism
Congenital Anorectal anomalies – Rectal agenesis, imperforate anus Spina bifida – Meningocele, meningomyelocele	Sphincter weakness, impaired anorectal sensation, loss of stool awareness, pudendal neuropathy
Trauma (including surgery) to pelvic floor muscles, pudendal nerve, and the spinal cord Anorectal surgery Colon resection Pelvic and anorectal trauma, spinal trauma Vaginal delivery – Spontaneous or assisted	Possible sphincter weakness, pudendal neuropathy, impaired rectal accommodation
Neurological impairment Cerebrovascular accident Dementia (Alzheimer's disease, multi-infarct dementia, normal pressure hydrocephalus) Diabetes mellitus Intracranial injury Meningoencephalitis Multiple sclerosis Neoplasm (brain, spinal cord) Pudendal neuropathy due to trauma or traction injury Spina bifida (meningocele, meningomyelocele)	Impaired anorectal sensation, pelvic floor dysfunction, loss of stool awareness, impaired rectal accommodation
Miscellaneous Anorectal prolapse Fecal impaction Malabsorption Medications (anticholinergic agents, antidepressants, caffeine, laxatives, muscle relaxants) Physical disabilities (due to aging, disease, or trauma) Proctitis (inflammatory bowel disease, radiation) Psychiatric disorders	Pelvic floor dysfunction, altered stool characteristics, anorectal hypersensitivity, wilful soiling, functional incontinence

Underlying IBD, diabetes mellitus, or malabsorption should be treated [28]. Agents precipitating inappropriate stooling (laxatives) are avoided. Increasing dietary fiber improves stool consistency; antidiarrheal agents reduce frequency and urgency in stooling [30]. Patients with fecal impaction benefit from disimpaction through suppositories, enemas, or manual evacuation, followed by using stool softeners and laxatives (polyethylene glycol), bowel retraining (regular toilet use after meals), and treating underlying behavioral problems.

Biofeedback (neuromuscular training) is a first-line treatment option in motivated patients with some preserved sphincter tone and impaired rectal sensation not responding to conservative measures [30]. It is often combined with pelvic floor muscle exercises and stimulation to enhance pelvic floor strength.

Disposable anal plugs alleviate fecal leak and seepage but are difficult to tolerate. Injecting biocompatible material into the anorectal submucosa or the intersphincteric space augments the perianal/perirectal tissue and approximates the anal mucosa, thereby closing the anal canal and/or raising the anorectal pressure to avert fecal incontinence [30]. Short-term improvement is noticed in over half of patients [31].

Surgery should be considered in patients who have failed conservative measures and neuromuscular training. Patients with significant symptoms and a defined defect of the external anal sphincter benefit from sphincteroplasty by plication or imbrication (85% good to excellent short-term

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results; 10–14% sustained improvement at 5 years) [30]. Those with more extensive sphincter damage may need an autologous gracilis or gluteus muscle transfer (dynamic graciloplasty) or implantation of an artificial bowel sphincter. Both procedures have significant potential complications, and long-term outcomes are not encouraging. Sacral nerve stimulation, in which electrodes are implanted in the second and third sacral nerve roots, stimulating the muscles of the pelvic floor appears to achieve greater than 50% improvement in most (89%) patients and full continence in over a third (36%) of patients [30, 32]. Children and patients with neurological disorders benefit from an antegrade continent enema procedure that offers periodic colon washout through an appendicostomy or a cecostomy. Permanent fecal diversion is another alternative in paralyzed, immobile patients with non-healing decubitus ulcers.

Rectal Prolapse

Background

Rectal prolapse is defined as protrusion of the layers of the rectal wall through the anal canal. The prolapse may be mucosal (partial), when only the mucosal and submucosal layers protrude, or full thickness (complete), when all layers overhang the anal canal [33]. It is seen more often among older women (sixfold increase compared to men); men tend to present at younger ages. Rectal prolapse is thought to commence as an intussusception from the rectosigmoid region at the level of the peritoneal reflection, progressing distally through the anal canal on continued exertion. Multiple factors predispose to rectal prolapse (Table 3).

Diagnosis

Patients present with dull perianal pain, rectal bleeding or mucorrhea, and fecal/urinary incontinence. Irreducibility and strangulation of the prolapsed segment cause severe and persistent perianal and abdominal pain and distention, fever, vomiting, and diaphoresis; gangrene may supervene. Perianal inspection is best accomplished with the patient sitting or squatting, and it assists in differentiating full-thickness prolapse from mucosal prolapse or prolapsed hemorrhoids [34]. Mucosal prolapse is thin and often segmental; full-thickness prolapse may be segmental or circumferential, plum colored with concentric mucosal folds. Prolapse longer than 5 cm usually contains a fold of peritoneum; larger prolapses contain small bowel. DRE identifies anal sphincter hypotonia; anoscopy may reveal a solitary rectal ulcer, present usually on the anterior rectal wall in 10–15% of patients [34]. Imaging studies, colonoscopy, and urodynamic studies are useful in further defining the diagnosis and identifying coexisting cystocele or colorectal pathology [34]. Physiologic tests (anorectal manometry, electromyography, and pudendal nerve testing) help identify and evaluate associated pelvic floor dysfunction and colonic inactivity [34].

Treatment

Non-operative approach yields poor results [34]. Increased fiber intake, fiber supplements, and stool softeners improve constipation, minimize straining, and may help heal rectal ulcers. Biofeedback is useful in retraining and enhancing sphincter function and improves continence and constipation following surgery [35]. Rubber band ligation or trans-anal excision is beneficial in patients with second−/third-degree mucosal prolapse without ulceration [36].

Transabdominal rectopexy is the procedure of choice in patients with full-thickness rectal prolapse, considered suitable for laparotomy [34, 37]. Laparoscopic approach has fewer postoperative complications and a shorter hospital course when compared with open rectopexy. Prosthetic meshes (polypropylene, polytetrafluoroethylene) are used to reinforce attachment of the mobilized rectum to the sacral promontory, inducing fibrosis and minimizing risk of recurrent prolapse and fecal incontinence. Rectopexy also helps heal

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Table 3 Common causes of rectal prolapse in infants/children and adults

Infants/ children	Cystic fibrosis Disturbances in bowel function (chronic diarrhea, constipation) Hirschsprung's disease Parasitic infestations Poor nutritional status Neoplasms (polyps) Neurological disorders (spina bifida, meningocele, meningomyelocele)
Adults	Aging (age-related tissue degeneration, weakness, and intercurrent illness) Cerebrovascular accident Dementia Increased intra-abdominal pressure (chronic constipation, chronic cough, heavy lifting, obesity) Multiparity (direct injury to pelvic floor muscles, nerves, and connective tissues caused by maternal expulsive forces). Large fetus, prolonged second stage of labor, episiotomy, anal sphincter laceration, epidural analgesia, operative deliveries, and oxytocin use are also considered risk factors Pelvic floor muscle weakness following spinal or pelvic trauma including surgery Psychiatric illness Pudendal neuropathy

Information from multiple sources

rectal ulcers. Coexisting uterovaginal prolapse may also be corrected (rectocolpopexy).

Perineal procedures (mucosal sleeve resection, Delorme procedure (mucosal sleeve resection and imbrication of the muscularis mucosa), perineal proctosigmoidectomy (Altemeier procedure involving trans-anal full-thickness resection of the prolapsed rectum and coloanal anastomosis)) are useful in older patients with multiple comorbidities unfit for laparotomy. Patients with short, full-thickness rectal prolapse may undergo the Delorme procedure; longer-segment prolapses require a proctosigmoidectomy.

Pruritus Ani

Background

Intense perianal itching (pruritus ani) is experienced by 1–5% of people, more often by men (2–4 times more common) between 30 and 60 years of age [38, 39]. The long-standing itch-scratch cycle eventually causes dryness and hyperpigmentation, infection, ulceration, and scarring of the involved skin. Irritability and depression often coexist [39]. Pruritus ani may be idiopathic; though in up to three-fourths of patients, an underlying local or systemic cause may be identified [40].

Causes

Hemorrhoids (20%), anal fissure (12%), idiopathic proctitis (6%), and condyloma/ulcerative proctitis (5%) are the predominant causes [38]. All these pathologies produce mucus or fecal soiling, initiating or aggravating the pruritus. Other causes include atopic and contact dermatitis, bacterial and fungal skin infections, clothing (retains moisture), medications (antibiotics, colchicine, laxatives, steroids), other dermatologic pathology (psoriasis, lichen planus, lichen sclerosis), parasitic infestations, systemic diseases (diabetes mellitus, hepatorenal disease, anemia, hyperthyroidism, and underlying anxiety), and various foods (alcohol, caffeinated drinks, chocolate, citrus fruits, milk products, peanuts, spices) [40].

Diagnosis

Diagnosis is usually based on history and examination focusing on the gastrointestinal tract and skin, including nails. The perianal region is closely inspected for primary perianal pathology and skin changes. Bacterial/fungal cultures and patch or Scotch tape testing establish the diagnosis of infections, parasitic infestations, or contact dermatitis. Endoscopy and biopsy are useful in diagnosing colitis. Manometric studies help

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diagnose motility disorders. Perianal skin biopsies may be required when the diagnosis is obscure or if a premalignant or cancerous lesion is suspected.

Treatment

The principles of management include ruling out secondary causes, eliminating all irritants (soaps, talcum powders, certain foods and fluids), avoiding trauma (scratching, vigorous scrubbing, using toilet paper), keeping the perianal skin clean and dry (cotton underclothes changed daily to minimize moisture accumulation, washing with water after stooling, and drying the skin), and ensuring regular bowel movements and normal consistency stool (increasing dietary fiber and adequate fluid intake) [41]. Using white, undyed, unscented toilet tissue minimizes allergic skin reactions. Those with diurnal hyperhidrosis should be encouraged to change their underclothes frequently to restrict perianal moisture accumulation. Low-potency steroids may help break the itch-scratch cycle. Underlying psychiatric issues (anxiety, obsessive-compulsive disorder) need treatment. Mittens or socks over hands may reduce nocturnal scratching. Vaseline may be applied locally if the skin is dry and thickened.

Topical capsaicin cream diluted in paraffin applied three times daily over 4 weeks relieves intractable perianal pruritus in over 70% of patients [42]. Perianal intradermal injection of methylene blue (15 ml of a 1% solution diluted with 0.5% lidocaine) also eases symptoms in a majority (60%) of patients with intractable pruritus, the improvement persisting over 4 years [43]. Tacrolimus ointment (0.035–0.1% applied 1–2 times daily) has also been shown to improve symptoms [41].

Infectious Proctitis

Background

Proctitis is defined as an inflammation of the anorectal mucosa, usually seen in adult males. Causes include sexually transmitted diseases (STDs – gonorrhea, chlamydia, syphilis, genital herpes), chemical irritation, IBD, ischemia, radiation, trauma, and miscellaneous causes (immune deficiency, vasculitis, other infections – amebiasis, *Clostridium difficile* infection, campylobacter infection) [44]. Radiation proctitis may be acute or chronic, and its incidence is probably related to radiation dosage, area of exposure, method of delivery, and use of cytoprotective agents [45].

Diagnosis

Patients usually present with perianal or lower abdominal pain, blood or mucus per rectum, change in bowel habits (diarrhea or constipation), sense of incomplete defecation, and tenesmus. Abdominal examination may show lower abdominal fullness and tenderness. Proctosigmoidoscopy may reveal mucosal edema, erythema, friability, bleeding, ulceration, inflammatory exudate, or herpetic vesicles limited to the anorectum. In chronic radiation proctitis, mucosal pallor, changes in vascularity, strictures, ulcerations, and fistulas may be seen [45]. The anal discharge can be analyzed (gram stain, nucleic acid detection and DNA amplification tests, and bacterial, fungal, or viral cultures) to identify specific infections. Stool studies (ova, cysts, parasites, *Clostridium difficile* toxin, and antigen) also help diagnose bacterial infections and parasitic infestations [46]. Endoscopy is useful in detecting proximal bowel involvement, especially in IBD; biopsies may be obtained for confirmation. Contrast imaging assists in detecting obstruction and fistula formation – consequences of IBD and radiation.

Treatment

The principles of management include providing symptomatic relief and addressing primary causes (Table 4). Antispasmodics and a low-residue diet relieve diarrhea and tenesmus. Steroid or mesalamine enemas are useful in patients with IBD. Antibiotics and antivirals administered appropriately help resolve specific infections [46]. Campylobacter proctitis and acute radiation

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Table 4 Treatment options in proctitis Refs. [44–48]

General measures	Hydration, analgesics, and antidiarrheals in acute proctitis Low-residue diet Antispasmodics
Cause-specific treatment	
Campylobacter infection	Erythromycin 500 mg twice daily for 5 days
Chlamydia infection	Doxycycline 100 mg orally twice daily for 7 days. Three-week therapy in men intimate with men and if HIV+
Crohn's colitis/proctitis	5-ASA (foam, gel, suppository, enema) Oral mesalamine 2.4 G daily in divided doses Topical steroids (enemas, foam, suppositories) In patients failing to respond to topicals – Oral 5-ASA/mesalamine Oral prednisone (20 to 60 mg daily) – In patients not responding to topical steroids Azathioprine 1.5–2.5 mg/kg/day orally – Patients not responding to or dependent on steroids. Used as steroid-sparing therapy
Giardiasis	Metronidazole 750 mg orally three times daily for 10 days followed by paromomycin 25–30 mg/kg per day three times daily for 7 days for eradication of cysts in bowel lumen
Gonococcal proctitis	Ceftriaxone 250 mg IM once + doxycycline 100 mg orally twice daily for 7 days
Herpes simplex proctitis	Acyclovir 400 mg three times daily for 7–10 days Famciclovir 250 mg three times daily for 7–10 days Valacyclovir 1G orally twice daily for 7–10 days
Shigella infection	Ciprofloxacin 500 mg orally twice daily for 7 days
Radiation proctitis	
Grade 1 [a]	Watchful waiting
Grades 2 and 3	Anti-inflammatory agents (oral sulfasalazine or mesalamine, steroid enemas, oral steroids, oral metronidazole) Antioxidants (vitamins A, C, E)
Grades 2 and 3 (no response to anti-inflammatories)	Rectal sucralfate or pentosan polysulfate Short-chain fatty acid enemas Hyperbaric oxygen at 2 atm for 90 min
Grade 3 (no response to above measures)	Chemical cauterization – Formaldehyde 10% applied for 2–3 min Endoscopic coagulation Argon or YAG laser photocoagulation
Grade 4	Surgery (fecal/urinary diversion, local excision, stricturoplasty, pelvic exenteration). Often requires reconstruction using vascularized flaps

[a]Grading based on intensity of symptoms, degree of ulceration and stricture, and presence of complications (hemorrhage, fistula, perforation, obstruction). Grade 0, no symptoms; grades 1–3, increasing intensity of symptoms; grade 4, uncontrollable pain/urgency or development of complications; grade 5, sepsis, multiple organ failure usually resulting in demise

proctitis are usually self-limiting; the latter resolves with discontinuing radiation for short periods. Chronic radiation proctitis may require more intensive management depending on its extent (grade) and symptomatology and may involve the use of anti-inflammatory agents (oral sulfasalazine with steroid enemas), sucralfate enemas, short-chain fatty acid, or pentosan polysulfate enemas or oral metronidazole. Antioxidants (vitamins A, C, and E) reduce diarrhea and tenesmus and supplement the beneficial effects of other treatment measures [45]. Hyperbaric oxygen, administered at 2 atm daily five times a week, improves symptoms probably by enhancing tissue oxygenation, impeding bacterial overgrowth and toxin production, and stimulating angiogenesis [47]. Topical formalin (10%) applied during proctosigmoidoscopy cauterizes and seals the fragile vessels in radiation-damaged tissues. Endoscopic electrocoagulation and laser photocoagulation are other options to control refractory bleeding. Surgery is reserved for patients with uncontrollable pain, fistula, bleeding, fecal incontinence, and obstruction and may

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involve a diverting colostomy, stricturoplasty, or pelvic exenteration [45, 48].

Hidradenitis Suppurativa

Background

Hidradenitis suppurativa is a chronic recurrent inflammatory skin disorder affecting the hair and areas containing apocrine sweat glands and adjacent connective tissue; perineal involvement occurs more often in men [49]. Pathophysiology involves occlusion of the ducts of the hair follicles, stasis and dilatation of the apocrine glands, secondary bacterial infection, abscess formation, development of sinuses and fistulas, and ultimately fibrosis and hypertrophic scarring. Cryptoglandular infections or Crohn's disease may coexist.

Diagnosis

Diagnosis is clinical and based on the characteristic history and physical findings of chronically draining sinuses with malodorous discharge and hypertrophic skin [7]. Proctosigmoidoscopy may show evidence of anal gland infections or IBD. Incontinence, lymphedema, and malignant transformation to squamous cell carcinoma (rare) are all possible sequelae.

Treatment

Treatment is usually prolonged and unsatisfactory in advanced stages. Broad-spectrum antibiotics (clindamycin, tetracyclines, rifampin) administered orally or applied topically reduce pain, redness, and discharge. Abscesses need drainage and sinus tracts may be de-roofed or marsupialized. Isotretinoin is useful, though contraindicated in women of childbearing age due to potential teratogenicity. Immunosuppressants (steroids, cyclosporine, infliximab, etanercept) also show promise but increase risk of concurrent infections and malignancy. Radiation, cryotherapy, and laser surgery are other options. Wide excision of the involved skin and underlying connective tissue followed by skin grafting or flap closure may be necessary in recalcitrant disease and, rarely, may also require temporary fecal diversion [49].

Condyloma Acuminatum

Background

Anal condyloma acuminatum (warts) is caused by sexual (usual) or nonsexual transmission of the human papillomavirus (HPV); most (>95%) are caused by types 6 and 11 [50]. These warts are more frequent in men who have sex with men and practicing receptive anal intercourse, in those with multiple sexual partners, and in the immunosuppressed, in whom the warts are more aggressive, relapse earlier, and are more often dysplastic [7]. Buschke-Löwenstein tumor (giant condyloma acuminata) is a rare and rapidly progressing variant, locally invasive, causing extensive destruction of surrounding tissue [7].

Diagnosis

Perianal warts are typically asymptomatic, but depending on the size and location of the warts, they may cause pain, itching, drainage, foul odor, bleeding, or dyschezia. Patients may also exhibit anxiety, guilt, anger, and loss of self-esteem [50]. Anal warts may be perianal or intra-anal; the diagnosis is made by visual inspection [46]. The lesions are usually found over sites traumatized during intercourse, vary from 5 to 15 in number, and, occasionally, coalesce into plaques (more common in diabetics and the immunosuppressed) [50]. Proctoscopy displays the intra-anal condyloma, usually confined below the dentate line. Biopsy confirms the diagnosis and rules out malignancy, and HPV typing categorizes the lesion as pertaining to low- and high-risk subtypes. Biopsy is, however, required only in failure of response to usual treatment measures, if dysplasia or malignancy is suspected, or in immunosuppressed patients. Complete

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genital examination should be performed to check for penile, scrotal, and cervicovaginal lesions; women should be offered a Papanicolaou (PAP) smear. Anal warts in children should arouse suspicion of sexual abuse, though vertical transmission at birth is possible.

Screening, Prevention, and Treatment

Current sexual partners as well as partners within the last 6 months should be screened for warts and other STDs. Condom use should be encouraged to minimize recurrence and infecting partners. Smoking cessation measures should be implemented. Both sexes between 9 and 26 years of age should be offered the quadrivalent HPV vaccine (Gardasil) to prevent infection by high-risk strains 6, 11, 16, and 18 [7, 50].

Multiple patient-applied local therapies (podofilox 0.5% solution or gel applied twice daily for 3 days a week (four such cycles), imiquimod 5% cream applied daily at bedtime for 16 weeks, sinecatechin 15% ointment applied three times daily for 16 weeks) are available [7, 46, 50]. They may all cause local redness, burning, induration, and ulceration. Both sinecatechin and podofilox are not yet considered safe for use during pregnancy. Clearance rates of 40–70% have been noticed with these treatment modalities [50]. Office therapies include application of acetic acid solutions, cryotherapy and electrosurgery, laser surgery, or scissor excision. Trichloro- or bichloroacetic acid 80–90% solution applied weekly works by coagulating proteins and is safe for use during pregnancy. Cryotherapy using liquid nitrogen is also safe during pregnancy but may also need to be repeated at regular intervals. Pain, irritation, and drainage are side effects of the treatment. Response rates parallel that of patient-applied therapies. Electrosurgical excision and destruction (fulguration) are also effective for removing condyloma. The smoke plume generated during destruction carries HPV particles; hence, there should be appropriate smoke evacuation techniques, and both patients and healthcare providers should wear masks to prevent inhalation of the particles. Scissor excision under local anesthesia using lidocaine with epinephrine to minimize pain and bleeding is useful where smaller numbers of lesions are involved. Both electrosurgery and sharp excision have high success rates (90–100%). Larger warts, especially in children, intra-anal warts, and Buschke-Löwenstein lesions require excision under general anesthesia. Recombinant interferon alpha may be injected under lesions or used as adjuvant therapy after surgical excision or fulguration [46, 50–51].

Anal Canal Cancers

Squamous cell carcinoma (SCC) is the most common type of malignancy in the anal canal (80%) followed by adenocarcinomas (16%) [7]. A strong causal relationship (86–100%) exists between oncogenic strains of HPV (types 16 and 18), immunosuppressive states (HIV, autoimmune diseases, transplant recipients), and SCC. Anal intraepithelial neoplasias (high grade, low grade) are precursors of SCC; the risk is higher in HIV-positive individuals, males in mutual conjugal relationships, and women with history of cervical dysplasia [51]. Screening high-risk populations with anal cytology or high-resolution anoscopy is a consideration. Universal vaccination against HPV in both sexes under 26 years of age is strongly recommended for primary prevention of premalignant lesions.

Half of patients with SCC manifest localized disease, the rest with regional nodal or distant metastases. Most patients with anal canal cancers present with a slow-growing intra-anal or perianal mass, bleeding (most common symptom – 45%), discharge, pain, and occasionally inguinal lymph node or intra-abdominal masses due to hepatic metastases. The diagnosis is evident in most patients on examination of the perianal region, DRE, and anoscopy. Biopsies from the primary and enlarged inguinal nodes should be taken for confirmation of the diagnosis and spread. The extent of thoracoabdominal spread should be evaluated by imaging of the chest, abdomen, and pelvis; endoanal ultrasound and MRI delineate the extent of local spread into the sphincters and perirectal lymph nodes. Chemotherapy (mitomycin-C

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and 5-fluorouracil) and radiation are the recommended treatment modalities for both the anal canal primary and inguinal disease (80% complete response rates); small superficial node-negative localized lesions may be excised with a 1 cm margin. Cisplatin may be substituted for 5-fluorouracil. Abdominoperineal resection of the rectum and anal canal is an option in recurrent or persisting disease (seen in 20–30% of patients) and has a 50% cure rate [7]. Presence of distant metastases denotes poor prognosis with median survivals under 1 year. Continued surveillance after chemoradiation or surgery is recommended with history, physical examination including DRE and anoscopy, and imaging at regular intervals for 5 years. Systemic chemotherapy, metastasectomy, and epidermal growth factor inhibitors are treatment options in those with widespread disease.

Melanoma of the anal canal usually has a poor outcome as most patients have widespread metastases at the time of diagnosis. Wide excision or abdominoperineal resection may be offered for local control in patients with disseminated disease.

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Colorectal Cancer

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General Principles

Colorectal cancer (CRC) is the third most common cancer in men after lung and prostate cancer and women after breast and lung cancer [1]. In 2019, the American Cancer Society estimated that 101,420 cases of colon cancer and 44,180 cases of rectal cancer would be diagnosed, and 27,640 men and 23,380 women would die from CRC [1]. The mortality from CRC has been decreasing for several decades due to improved CRC screening, risk factor modification, and better treatments. Over the last 15 years, the incidence of CRC in adults 55 years and older decreased by 3.7% per year, while the incidence in adults less than 55 years old decreased by 1.8% [1].

The majority (70%) of CRC cases are sporadic disease, i.e., no family history of CRC, while only 30% of CRCs have a genetic predisposition. The multistep progression from normal colonic epithelium to invasive cancer involves an intermediate precursor, the adenomatous polyp. CRC screening may detect and remove this adenomatous polyp and detect early CRCs when treatment is most successful. Most organizations recommend that CRC screening starts between ages 45–50 and continue up to ages 75–85 [1].

Adenomatous polyps are typically asymptomatic. As the polyp to carcinoma cycle progresses, it is more likely to cause rectal bleeding, change in bowel habits, weight loss, anorexia, abdominal pain, or anemia, which may result in fatigue and weakness [1]. For most patients with localized CRC, surgery is the most common treatment. When CRC has local or distant metastasis, treatment may involve surgery, chemotherapy, targeted immunotherapy, and radiation.

Risk Factors

There are known risk factors that increase the chances of developing CRC. Modifiable factors include obesity and smoking, while genetic factors include hereditary conditions, personal or family history of CRC (Table 1).

Polyps

Polyps are fleshy growths that occur in the lining of the colon (Fig. 1). Polyps represent the most significant single risk factor for developing CRC. Polyps are classified as hyperplastic, neoplastic (adenomatous and malignant), hamartomatous, and inflammatory. The malignant potential of neoplastic polyps depends on the type and degree of dysplasia and the polyp's size.

Polyps with malignancy risk include adenomatous polyps, which have three histologic variants (Table 2) and sessile serrated adenomas (SSAs). SSAs may progress to dysplastic lesions, leading to unstable microsatellite carcinomas [2]. Polyps more than 2 cm in size have more than a 40% chance of malignancy [3].

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Table 1 Factors that increase the risk of colorectal cancer

Modifiable factors	Hereditary and medical factors
Obesity	Personal or family history of CRC or adenomatous polyps
Physical inactivity	Certain genetic conditions
Long-term smoking	Personal history of inflammatory bowel disease
High consumption of red or processed meat	Type 2 diabetes
Low calcium intake	
Moderate to heavy alcohol consumption	
Very low intake of fruits and vegetables	
Low intake of whole-grain fiber	

Source: [1]

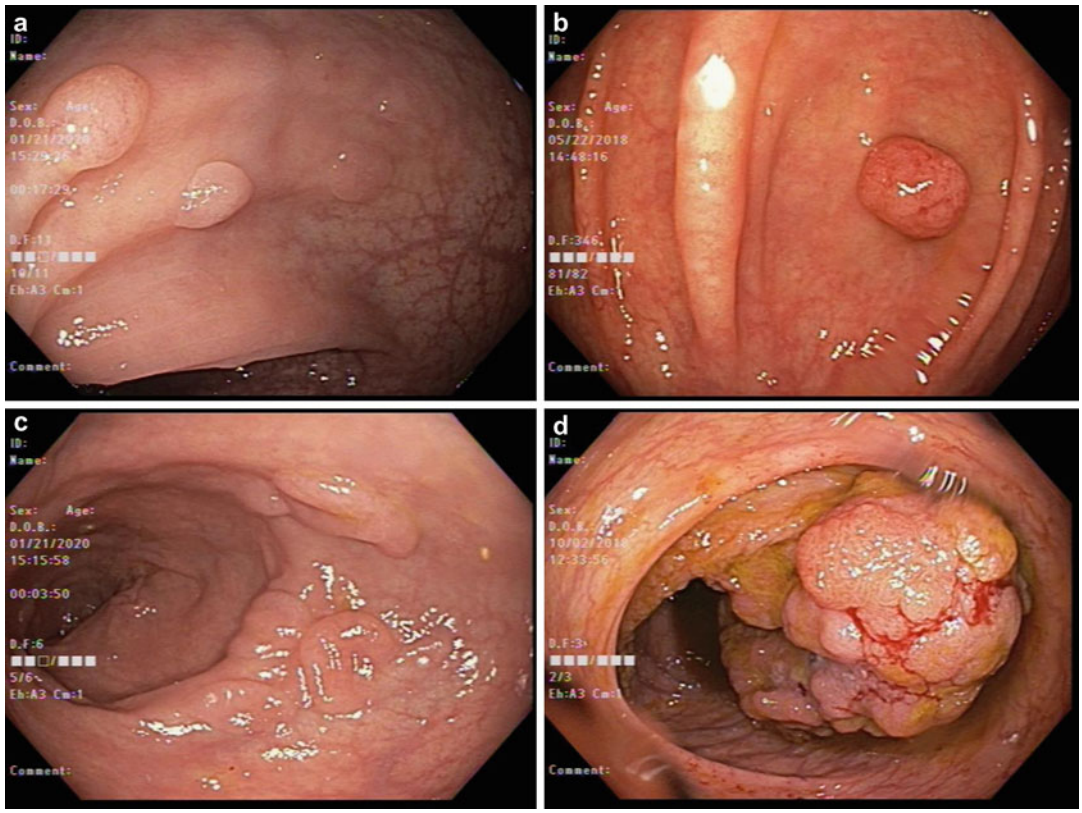


Fig. 1 Colonoscopy images showing colonic polyps and adenocarcinoma. (**a**) Hyperplastic polyps. (**b**) Tubular adenoma. (**c**) Sessile serrated adenomas. (**d**) Invasive adenocarcinoma. (Source: Original)

Genetics

Lynch Syndrome

Hereditary CRC syndromes contribute to about 5% of all CRCs [4]. At least one-fourth of CRC patients have a positive family history for CRC [4]. Lynch syndrome is the most common cause of hereditary CRC, accounting for 2–4% of all CRC cases. Lynch syndrome is an autosomal dominant syndrome caused by a mutation in one of five genes that results in interference with DNA repair. The lifetime risk of CRC in Lynch syndrome is estimated to be 40–60%. It is also associated with an increased risk of several other cancers,

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Table 2 Types of adenomatous polyps and malignant potential

Adenoma type	Prevalence (%)	Risk of malignancy (%)
Tubular	75–85	<5
Tubulovillous	10–15	20–25
Villous	5–10	35–40

Source: [3]

including endometrial, ovarian, gastric, hepatobiliary, and urinary tract malignancies [4].

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is the second most common underlying cause of hereditary CRC, causing around 1% of all CRC. It is also an autosomal dominant condition. FAP is caused by germline mutations in the APC tumor suppressor gene and results in hundreds or thousands of adenomatous polyps throughout the colon. Approximately 25% of FAP patients are the result of de novo mutations rather than familial inheritance [4].

Other Hereditary Syndromes

MUTYH associated polyposis (MAP) is an autosomal recessive defect in DNA oxidative injury repair. Patients with MAP develop numerous colonic polyps, but many fewer than in FAP. Hamartomatous polyposis syndrome and serrated polyposis syndrome are hereditary conditions that increase the risk for CRC [4].

Tobacco

Smoking increases the risk of adenomas. A meta-analysis of 42 observational studies found pooled risk estimates for current, former, and ever smokers compared with never smokers for the development of adenomatous polyps were 2.1, 1.5, and 1.8, respectively. This study found that the association was stronger for high-risk compared to low-risk adenomas and concluded that smoking is associated with the formation and aggressiveness of adenomas [5].

Alcohol

Alcohol consumption of 2 or more drinks per day (> 30 g/d) is associated with increased risk for colorectal cancer. Compared with nondrinkers, the relative risk for colorectal cancer is 1.2 for persons consuming 30 to 45 g/d and 1.4 for persons consuming 45 g/d or greater [6]. A retrospective cohort analysis of 1448 patients found that significant alcohol consumption increased the risk of adenoma formation (adjusted hazard ratio of 1.86) [7].

Comorbidities

Obesity

Obesity (body mass index (BMI) exceeding 30 kg/m^2) and being overweight (BMI 25–29.9 kg/m^2) are modifiable risk factors for CRC. A systematic review and meta-analysis of prospective studies, including 12,837 CRC cases among 1,343,560 participants, found that waist circumference (RR 1.42) and waist-to-hip ratio (RR 1.39) were significantly associated with CRC [8]. A case-control study of 693 patients referred to a colonoscopy unit found that the incidence of overweight and obesity was significantly higher in adenoma patients than controls (49.9% versus 0.9%, p-value = 0.04) [9].

Diabetes Mellitus

A case-control study of 693 individuals found a significant association between diabetes and adenomatous polyps (OR 1.83, p-value = 0.023) [9]. A meta-analysis of case-control and cohort studies found that diabetes was associated with an increased risk of colon cancer (RR 1.4) and rectal cancer (RR 1.20) [10].

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Pathogenesis

There are three main pathways by which cancers arise in the colon: chromosomal instability (CIN), CpG island methylator phenotype (CIMP), and microsatellite instability (MSI) [11]. These mechanisms overlap in the carcinogenesis of CRC. With CIN, there is a mutation in the adenomatous polyposis coli (*APC*), then the activation of oncogene KRAS and inactivation of tumor suppressor gene, TP53. About 85% of the sporadic tumors and the gemline APC gene mutation seen in FAP involve aneuploidy and loss of heterozygosity. The CIMP pathway involves the hypermethylation of tumor suppressor genes, particularly MGMT and MLH1. BRAF mutation and microsatellite instability are involved with this process of hypermethylation. With the MSI pathway, there is a disruption in the activation of genetic alterations, where there had been a DNA mismatch requiring a mismatch repair. Familial Lynch syndrome is an example of the MSI pathway. The hypermethylation of the MMR gene can also lead to MSI. MSI tumors are often poorly differentiated, though with better prognosis, and are often located in the proximal colon [11].

Approach to the Patient

Choosing a Screening Modality

There are several widely accepted modalities to screen for CRC. The choice of screening tests depends upon availability, patient preference, cost, and individual patient risk. A US Multi-Society Task Force on CRC concluded that a risk-stratifying strategy, offering multiple options and allowing the patient to choose, and sequentially offering tests beginning with a preferred test are all acceptable strategies for selecting a screening modality [12]. There are three broad categories of screening modalities: stool-based, radiographic imaging, and endoscopy [13].

Stool-Based Screening

Stool-based screening modalities considered acceptable by the USPSTF include annual Guaiac fecal occult blood tests (gFOBT), annual fecal immunochemical tests (FIT), and FIT-DNA every 1–3 years [14]. gFOBTs have a sensitivity of over 70% and a specificity of over 90%. However, they require dietary restrictions and multiple samples to be turned in. FIT do not require dietary restriction, and only one sample is needed. Sensitivity is around 80%, and specificity is as high as 94% [15]. FIT-DNA combines occult blood testing with testing for DNA alterations known to be associated with CRC. FIT-DNA is more sensitive than FIT for detecting CRC and precancerous lesions [15]. FIT-DNA is considerably more expensive than FIT or gFOBT [12].

Radiographic-Based Screening

The USPSTF also approves CT colonography every 5 years [14]. The American College of Radiology has given CT colonography every 5 years an Appropriateness Category of "Usually Appropriate" for CRC screening of both average and moderate-risk individuals [15]. CT colonography has a 93% sensitivity and a 97% specificity for polyps 10 mm or greater [15]. A barium enema is not recommended for CRC screening.

Endoscopic-Based Screening

Colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, and a combined strategy of sigmoidoscopy every 10 years plus annual FIT are endoscopic modalities considered acceptable by the USPSTF [14, 16]. Colonoscopy is regarded as the ideal screening method. Compared to colonoscopy, the disadvantage of flexible sigmoidoscopy is that proximal lesions may be missed. Capsule endoscopy is not FDA approved for screening average-risk individuals for CRC [12].

Serum-Based Screening

The Septin9 assay is an FDA-approved serum test for CRC screening [12]. Septin9 has a sensitivity for CRC of 48%, but no sensitivity for polyps [17]. It is also relatively expensive compared to FIT [17]. In 2017, a US Multi-Society Task Force recommended against using Septin9 for CRC screening [12].

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Average Risk Screening

For average-risk patients, patient preference, financial considerations, and test availability should be factored into the choice of which screening method to use [18]. As an alternative to universal screening, risk calculators (https://qcancer.org/15yr/colorectal/) are available to help clinicians and patients understand their risk to decide whether or not to screen for CRC. Using such a calculator, some experts suggest using a three percent 15-year risk as to the cutoff for screening [19].

Many organizations have produced screening guidelines for patients at average risk for CRC (Table 3). There are some notable differences in these recommendations. Most major authorities recommend screening from age 50–75, with several screening modalities being acceptable [19].

Table 3 Colorectal cancer screening recommendations by organization

Organization	Year of most recent update	Screening age	Recommended Test and Timing
American College of Gastroenterology	2009	Start at age 50	Colonoscopy every 10 years
US preventive services task Force	2016	Screening for ages 50–75; for ages 76–85, an individualized discussion	gFOBT or FIT every year
			FIT-DNA every 1–3 years
			FIT every year and sigmoidoscopy every 10 years
			Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
			CT colonography every 5 years
American college of physicians	2019	Ages 50–75; beyond age 75 with a life expectancy of 10 years or greater	High sensitivity gFOBT or FIT every 2 years
			Colonoscopy every 10 years
			Sigmoidoscopy every 10 years and FIT every 2 years
American Cancer Society	2018	Ages 45–75; for ages 76–85, an individual decision based on preference, life expectancy, and overall health	High sensitivity gFOBT or FIT every year
			FIT-DNA every 3 years
			Colonoscopy every 10 years
			CT colonography every 5 years
			Sigmoidoscopy every 5 years

Sources: [18, 45–47]

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Increased Risk Screening

Patients with a known genetic predisposition and those with at least one first degree relative with CRC are at increased risk and should be screened more aggressively. The US Multi-Specialty Task Force recommends that patients with a single first-degree relative diagnosed at age 60 or above begin screening at age 40. For these patients, the modality and frequency of testing are the same as average-risk individuals. However, for patients with more than one first-degree relative, or any first-degree relative diagnosed below age 60, it is recommended that screening starts at age 40 or 10 years earlier than the youngest relative at their age of diagnosis, whichever is earlier. Colonoscopy is the recommended modality for these patients [12].

Overview of Colonoscopy Procedure

Colonoscopy is the most widely used direct visualization screening method for CRC in the United States. It is usually performed in an ambulatory or hospital-based endoscopy suite. Colonoscopy can cause serious risks to include cardiopulmonary complications (0.9%), bowel perforation (less than 0.1%), hemorrhage (0.1% to 0.6%), infection (less than 0.1%), and post-polypectomy syndrome (2.9%) [20].

Bowel Preparations

Most patients must undergo bowel preparation for 1–2 days before colonoscopy. Diagnostic accuracy is dependent on the quality of colonic preparation and the skill of the endoscopist. Inadequate bowel preparation can lead to an inability to detect neoplastic lesions and increases the risk of adverse events during the procedure. A clear liquid diet is recommended 24–48 h before starting the bowel prep and using a colon cleansing agent. On the day of the procedure, the patient should be made "NPO" or take nothing by mouth. There are many commercial agents available, and suggested use is usually per provider preference and patient history (Table 4). If a patient has had unsuccessful and inadequate bowel preparation on one agent, it can be switched to another of a different class or used for a more extended period before a colonoscopy in the future. A split-dose prep involves giving half of the bowel preparation dose the day before the colonoscopy and the remaining dose on the morning of the procedure. There is evidence that split-dose prep results in a higher-quality colonoscopy examination than the ingestion of the entire preparation on the day or evening before colonoscopy [21].

Colonoscopy Overview

Patients should inform their provider of all prior conditions and medications before the colonoscopy. Aspirin and anticoagulants may need to be stopped before undergoing the procedure. Warfarin should be stopped 5–7 days before the procedure. New oral anticoagulants such as dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) should be held 48 h before the procedure; clopidogrel (Plavix) should be held 5 days before the procedure. If the patient has a high risk of a cardiac condition such as recent cardiac stenting, non-emergent colonoscopies should be postponed. Low-dose aspirin, i.e., 81 mg, can be continued prior to and after the procedure. Antibiotics are not recommended before colonoscopy. Colonoscopy is usually performed with the patient under conscious sedation for analgesic and anxiolytic control. Deep sedation, i.e., propofol administered by anesthesia personnel, may be considered if available but increases the cost of the procedure.

Quality Metrics for Colonoscopy

Adenoma detection rate (ADR) is the percentage of colonoscopies in which one or more adenomas were detected. ADR is dependent on the skill of the provider, positioning of the patient, withdrawal time, and bowel preparation, all affecting the ability to visualize the haustral folds completely. A ten times higher hazard ratio for

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Table 4 Common bowel preparations for colonoscopy

Brand	Composition	Recommended dosing	Additional fluid	Split dosing	Warnings
GoLYTELY	PEG, sodium sulfate, sodium, bicarbonate, sodium chloride, potassium chloride	4 l	None	2–3 l day before and 1–2 l day of procedure	
NuLYTELY; Trilyte	PEG, sodium bicarbonate, sodium chloride, potassium chloride	4 l	None	2–3 l day before and 1–2 l day of procedure	
Moviprep	PEG-3350, sodium sulfate, sodium chloride, ascorbic acid	2 l	1 l clear liquids	1 l day before and 1 l day of procedure	Avoid in patients with glucose-6-phosphate dehydrogenase deficiency
Suprep	Sodium sulfate, potassium sulfate, magnesium sulfate	12 oz	2.5 l water	6 oz. OSS with 10 oz. of water +32 oz. water day before and 6 oz. OSS with 10 oz. of water +32 oz. water day of procedure	
Suclear	Sodium sulfate, potassium sulfate, magnesium sulfate, PEG-3350	6 oz. oral sodium sulfate/ 2 l PEG-ELS	1.25 l water	6 oz. OSS with 10 oz. of water +32 oz. water day before and 2 l PEG-ELS day of procedure	
Prepopik	Sodium picosulfate, magnesium sulfate, anhydric citric acid	10 oz	2 l water	5 oz. Prepopik day before +40 oz. clear liquids and 5 oz. Prepopik +24 oz. clear liquids the day of the procedure	Avoid in patients with renal insufficiency
Osmoprep	Monobasic and dibasic NaP tablets	32 tablets	2 l water	20 tablets day before and 12 tablets the day of the procedure	Avoid in patients with renal insufficiency or risk factors for acute phosphate nephropathy; not recommended for routine use

Source: [21]
PEG polyethylene glycol, *ELS* electrolyte solution, *NaP* sodium phosphate, *l* liter, *oz.* ounces

interval cancer has been noted for colonoscopists with an ADR <20% compared to that for colonoscopists with an ADR >20% [22]. Providers aim to have a high ADR to increase CRC detection and reduce the risk of interval cancer. A low ADR is associated with increased rates of post-colonoscopy CRC. Recent guidelines suggest that colonoscopists should have an overall ADR of

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more than 25% (for men ≥30%, for women ≥20%) [22].

The cecum is identified once the colonoscope has reached the ileocecal valve and the entire medial wall of the cecum between the ileocecal valve and appendiceal orifice is visible. The cecal intubation rate (CIR) is the ratio of the number of screening colonoscopies that the cecum was visualized divided by the total number of screening colonoscopies. The CIR is a frequently used indicator for colonoscopy competency and an important quality metric. Guidelines suggest that the CIR of competent colonoscopists should be higher than 95% [22].

ADR and CIR are directly affected by bowel preparation. Complications associated with inadequate bowel preparation include incomplete colonoscopy, prolonged colonoscopy time, and reduced diagnostic yield [22]. The bowel preparation should be documented thoroughly and described at each part of the colon. Providers may use validated preparation scores such as the Boston Bowel Preparation Scale (BBPS) or the Ottawa Bowel Preparation Scale (OPBS) [23]. If bowel preparation is inadequate, then the procedure must be repeated within 6–12 months.

Workup of Individual Suspected of Colorectal Cancer

In individuals suspected or newly diagnosed with CRC, the next step in evaluating these patients is preoperative clinical staging. A complete history and examination should be completed looking for ascites, hepatomegaly, or lymphadenopathy. Helpful labs include carcinoembryonic antigen (CEA), a colon cancer tumor marker, complete blood count, BUN, creatinine, and liver enzymes. Computed tomography (CT) of the abdomen and pelvis is often obtained before surgery, as the results could influence the surgical approach. Chest imaging may be considered to exclude lung metastases, but its use is controversial. Positron emission tomography (PET) scans do not appear to be helpful in preoperative staging. PET scans are often not obtained except as an adjunct to other imaging in particular circumstances, i.e., in patients thought to be candidates for resection of liver metastasis of CRC.

TMN and Anatomic Stage

CRCs may spread by four methods: lymphatic, hematogenous, continuous, and transperitoneal. CRCs most commonly spread to lymph nodes, the liver, and lungs but may also spread to bone and brain. The tumor, node, and metastasis (TMN) staging system is the preferred staging system for CRC and older staging systems, i.e., Astler-Coller modifications of the Duke's classification are discouraged (Tables 5 and 6) [24].

Treatment

Endoscopic Therapy

Endoscopic polypectomy is a standard treatment option for colorectal neoplasia and decreases mortality from CRC. The aim of polypectomy is the complete removal of the polyp and prevention of further developing CRC. Polypectomy is performed using forceps, cold snare, and hot snare. The majority (80%) of all polyps recognized during colonoscopy are 1–5 mm in size, known as diminutive polyps, representing the majority of colorectal polyps [25]. The American Society for Gastrointestinal Endoscopy (ASGE) recommends the use of cold snare polypectomy for most diminutive polyps. Hot snare polypectomy is associated with the additional risk of thermal injury and a possible increase in bleeding. If necessary, cold forceps resection should be limited to small polyps (≤2 mm) and only to those anticipated to be resected in a single bite. For complex or excessively large polyps, i.e., >20 mm, endoscopic mucosal resection is recommended.

Surgery

Surgical resection is another treatment option for complex polyps not amenable to conventional

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Table 5 The TNM staging system

	Definition	Score
T	Tumor	Tx – Cannot be measured T0 – No evidence of a primary tumor Tis – Carcinoma in situ T1 – Cancer has grown through the muscularis mucosa into the submucosa T2 – Cancer has grown into the muscularis propria T3 – Cancer has grown into the outermost layers of the colon or rectum but has not gone through them T4a – Cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs T4b – Cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs
N	Nodes	Nx – Cannot be measured N0 – Nearby nodes do not contain cancer N1 – Has spread to 1–3 nearby lymph nodes N1c – Has spread into areas of fat near the lymph nodes but not the nodes themselves N2a – Has spread to 4–6 nearby lymph nodes N2b – Has spread to 7 or more nearby lymph nodes N3 – Metastasis in 7 or more regional lymph nodes
M	Metastasis	M0 – No distant cancer found M1 – Cancer has spread to distant organs or tissues

Source: [24]

Table 6 The American Joint Committee on Cancer (AJCC) and the TNM system

AJCC stage	TNM grouping
0	Tis, N0, M0
I	T1 or T2, N0, M0
IIA	T4a, N0, M0
IIB	T4b, N0, M0
IIIA	T1 or T2, N1/N1c, M0 **OR** T1, N2a, M0
IIIB	T3 or T4a, N1/N1c, M0 **OR** T2 or T3, N2a, M0 OR T1 **OR** T1 or T2, N2b, M0
IIIC	T4, N2a, M0 **OR** T3 or T4a, N2b, M0 **OR** T4b, N1 or N2, M0
IVA	Any T, any N, M1a
IVB	Any T, any N, M1b
IVC	Any T, any N, M1c

Source: [24]

polypectomy and is the primary curative method of CRC. Polyps with characteristics of deep submucosal invasion, which have been proven by advanced endoscopic imaging techniques, should be referred for surgery [25]. In patients with CRC, resection of the affected colon or rectum is recommended. To ensure that the tumor and its principal zone of lymphatic spread are removed, the dissection should ideally follow the embryological anatomical planes with special attention given to the circumferential resection margins [26]. Local lymph node metastasis can also be removed during laparoscopic surgery in most cases [25]. Surgery may be done either laparoscopically or open. Laparoscopic resection of CRC is as safe as open surgery [26]. Surgical success rates are highly dependent on preoperative staging, patient age, and comorbidities. CEA should be obtained before the surgery to serve as a baseline value for postoperative surveillance.

Chemotherapy and Radiation

Patients with stage 0 or I rectal or colon cancer do not typically require chemotherapy. Chemotherapy is controversial for stage II colon cancer but is frequently used in stage III colon cancer and is the mainstay of stage IV colon cancer therapy. 5-FU or capecitabine may be used in stage II rectal cancer, and these agents may be part of a regime for stage III or IV rectal cancer. Radiation therapy is considered in patients with stage III or IV colon cancer for those not considered surgical candidates or to treat symptoms, i.e., pain. Radiation therapy is typically used in combination with

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chemotherapy in patients with stage II–IV rectal cancers. Hepatic artery infusion or infusion of immunotherapy drugs may be considered in patients with stage IV colon or rectal cancer for treatment of metastases, i.e., liver metastases.

Postoperative Surveillance

The American Cancer Society recommends intensive postoperative surveillance, beginning 4–6 weeks after surgery, then every 3–6 months for the first 2–3 years, then every 6 months for 5 years. CEA testing is recommended at each visit. Routine testing other than CEA to monitor for recurrent disease is not recommended. Surveillance colonoscopy is recommended 1 year after initial treatment. If advanced adenoma (>1 cm with a villous component or high-grade dysplasia) is found, then colonoscopy should be repeated in 1 year. Otherwise, repeat surveillance colonoscopy in 3 years, then every 5 years. Patients with a higher risk of recurrence should be offered annual CT of chest, abdomen, and pelvis for 5 years after curative treatment for CRC. Routine CEA testing or CT scans after 5 years of initial treatment is not recommended [27].

Prognosis

The most important factor in the prognosis of CRC is the stage at presentation. Other important prognostic factors include the presence of extramural tumor, lymphovascular and perineural invasion, histologic grade, the preoperative level of CEA, microsatellite instability (MSI), and the RAS and BRAF mutations. There is a difference regarding the prognosis in the location of CRC, as left-sided (distal colon and rectal) CRCs versus right-sided (proximal colon) CRCs are associated with a better prognosis [28].

Prevention

Prevention of CRC can be approached from primary, secondary, and tertiary prevention. Primary prevention includes smoking cessation, reduction in alcohol usage, regular physical activity, and dietary modification. Secondary prevention aims to detect early disease by screening and to excise precancerous lesions. Individuals at high risk for CRC such as a family history of CRC, a personal history of ulcerative colitis or previous adenomas should have regular screening colonoscopies. Tertiary prevention is directed to the needed care post-CRC treatment, with the goal of improved outcomes and reduced risk of recurrence of CRC. Individuals may inquire about prevention strategies for CRC and polyps (Table 7).

Diet

There is good evidence that moderate daily intake of cow's milk reduces the risk of CRC [29]. There is no direct evidence that decreasing cholesterol, fat, or red meat intake reduces the risk for CRC or polyps. There is conflicting evidence for coffee intake, and there is strong evidence that increasing fiber intake does not reduce the risk of CRC or polyps [30, 31].

Lifestyle

There is good evidence that increasing physical activity decreases the risk of CRC, and there is indirect evidence that weight loss decreases the risk of CRC [32, 33]. There is fair to moderate evidence that moderate or higher alcohol intake and cigarette smoking increase the risk of CRC and polyps [5, 34, 35].

Medications

There is strong evidence that daily calcium use for 3–4 years decreases the risk of polyps and CRC [36, 37]. There is good evidence that daily statin use for at least 5 years decreases the risk of CRC and polyps [38]. Aspirin, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors decrease the risk of CRC or polyps; however, these medications are not recommended in the average-risk population due to the risk of GI

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Table 7 Summary of dietary, lifestyle, and medications to prevent colorectal cancer and polyps

Factor	Effect	Comment	Evidence
Diet			
Cholesterol and fat intake	Increased risk of CRC with increased cholesterol intake, and increased risk of serrated polyps with increased fat intake	There is no evidence that reduction in cholesterol or fat intake lowers risk of CRC or serrated polyps	One meta-analysis, one RCT, and one prospective study
Coffee consumption	Conflicting evidence	More research is needed from high-quality trials	One case-control study, one RCT, and one meta-analysis of prospective cohort studies
Dairy intake	Reduced risk of CRC with more than 8 oz. of cow's milk per day	Moderate daily intake of cow's milk reduced risk of CRC	Meta-analysis of 10 cohort studies
Fiber	No evidence for reduced risk of CRC or polyps with increasing fiber intake	Fiber from different sources was used	Two Cochrane reviews and 1 meta-analysis of 13 prospective studies
Red meat intake	Increased risk of CRC with increasing red meat and processed meat intake	There is no direct evidence that decreasing red meat and processed meat intake reduces risk of CRC and polyps	Meta-analysis of 13 prospective studies and meta-analysis of 34 case-control studies and 14 cohort studies
Lifestyle			
Alcohol intake	Increased risk of CRC and increased risk of serrated polyps	Evaluated effect of >15 g per day of beer, wine, or spirits	Large cohort study (CRC) and meta-analysis of 10 observational studies (serrated polyps)
Cigarette smoking	Increased risk of high-risk adenomatous polyps and CRC in current smokers	Strong association between smoking and high-risk adenomatous polyps and CRC; no direct evidence that smoking cessation decreases risk	Meta-analysis of 42 observational studies
Obesity	Bariatric surgery associated with reduced risk of CRC	Indirect evidence	Meta-analysis of four observational studies and a systematic review of 15 cohort studies
Physical activity	Decreased risk of colorectal cancer for occupational and recreational physical activity	Demonstrated benefit of increasing occupational and recreational physical activity for reducing the risk of colon and rectal cancers	Meta-analysis of 17 cohort studies and 21 case-control studies
Medications			
Antioxidants	No benefit for beta carotene; vitamins A, C, or E; or selenium	Not recommended to decrease the risk of CRC or adenomatous polyps	Meta-analysis of 20 RCTs
Aspirin	Reduced risk of CRC	Not recommended in the average-risk population because of the risk of GI bleeding and hemorrhagic stroke	Review of three RCTs
Calcium	Reduced risk of adenomatous polyps and reduced risk of CRC; no effect for serrated polyps	Calcium use for 3–4 years is recommended to decrease risk of CRC or adenomatous polyps but not serrated polyps	Cochrane review and meta-analysis

(continued)

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Table 7 (continued)

Factor	Effect	Comment	Evidence
Cyclooxygenase-2 inhibitors	Reduced risk of adenomatous polyps	Not recommended secondary to increased risk of GI and cardiovascular events	Two RCTs
Folic acid	Did not decrease risk of adenomatous polyps	Not recommended secondary to no benefit, more study needed	Single RCT
Hormone therapy	Reduced risk of CRC but no decreased risk of serrated polyps	Harms outweigh potential benefits, and routine use is not recommended at this time	Meta-analysis of four studies and one case-control study
Nonsteroidal anti-inflammatory drugs	Decreased risk of CRC	Not recommended secondary to increased risk of GI and cardiovascular events	Meta-analysis of 15 RCTs
Statins	Statin use associated with decreased risk of advanced adenomatous polyps and decreased risk of CRC	Effect observed in individuals who had used a statin for at least 5 years	Meta-analysis of six studies and one case-control study
Vitamin D	Conflicting evidence	More research is needed from high-quality trials	Guideline based on 3 RCTs and 28 observational studies, and meta-analysis of 18 observational studies

Source: [20]

bleeding, hemorrhagic stroke, and cardiovascular events [39–41]. Hormone therapy reduces the risk of CRC but is not recommended because the harms outweigh the benefits [42]. There is good evidence that beta carotene, vitamins A, C, or E, selenium, and folate are not effective for decreasing the risk of CRC or polyps [20].

Family and Community Issues

CRC has a better prognosis with early detection; therefore, screening should be recommended to all age-eligible individuals. State and national initiatives address public health strategies that promote primary prevention, cancer screening, early diagnosis, and access to effective evidence-based treatment and survivorship care [43]. Family physicians often play a key role in communities by encouraging the routine use of CRC screening and education. Individuals may fear undergoing a colonoscopy due to stigmatism or misconceptions about the procedure. Other screening modalities, such as fecal studies, should be offered when individuals decline screening colonoscopy. Educational pamphlets distributed or available at routine doctor's visits, community awareness events, support groups, and media campaigns can all contribute to promoting screening. For individuals diagnosed with CRC, social integration, and community support are essential. Research has established that strong social relationships predict lower all-cause mortality. The health risks associated with social isolation are comparable to traditional risk factors, such as smoking, blood pressure, and obesity. Large social networks may improve survival through increased support, including assistance in getting to medical appointments, reminders to take medications, and help with nutrition and mobility [44].

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Surgical Problems of the Digestive System

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Brian Coleman and Kalyanakrishnan Ramakrishnan

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Recent developments in the field of general surgery have generated significant innovations in the management of patients with abdominal pathology. Advances in imaging (FAST – focused assessment with sonography in trauma, computed tomography (CT) angiography) have enabled earlier and a more precise diagnosis to be made and minimized the role of exploratory surgeries for trauma. Minimally invasive (keyhole) and "robotic" surgeries have also provided greater precision in treatment while minimizing surgical trauma, enabling maximal postsurgical preservation of organ function and earlier patient return to normal activity. However, the cardinal surgical principles (judicious preoperative assessment, meticulous operative technique, and prevention of postoperative complications) remain unchanged.

Abdominal Pathology

The abdomen has long been considered a "Pandora's box," a cavity within which many varied and undetected pathologies may progress unchecked. Diseases of the digestive system comprised nearly eight million (6.1%) emergency room visits in 2010; over ten million patients (8%) sought emergency care for abdominal pain [1]. Apart from problems related to the abdomen and pelvis, pain from vertebral pathology radiating anteriorly may present with abdominal pain. Patients with cardiopulmonary diseases (pneumonia, pulmonary embolism, pneumothorax, acute coronary syndrome) may also present with upper abdominal pain, mimicking abdominal pathology. Abdominal wall pathology (Herpes Zoster, rectus sheath hematoma) and systemic diseases (diabetic ketoacidosis, porphyria, and sickle cell disease) may also present with abdominal symptoms [2, 3].

Some Key Terms and Maneuvers

Abdominal pain is the cardinal-presenting symptom, and the most confounding and potentially life-threatening complaint evaluated by an emergency room or family physician. Abdominal pain may be *acute* (lasting a week or less) or *chronic*. It

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may also be *parietal* (sharp, well-defined and localized, and usually due to inflammation of the parietal peritoneum) or *visceral* (ill-defined, dull and gnawing pain arising from the abdominopelvic viscera often associated with parasympathetic overdrive producing bradycardia, diaphoresis, and nausea). *Referred pain*, pain experienced at a site distant from the focus of involvement, follows nerve roots subserving intra-abdominal and other (usually cutaneous) regions converging at the same levels in the spinal cord. An "*acute abdomen*" is an intra-abdominal process (inflammation, infection, posttraumatic) producing acute abdominal pain and other symptoms requiring urgent evaluation, hospitalization, and often surgical intervention. *Guarding* is voluntary contraction of the abdominal wall muscles in response to underlying peritoneal/visceral irritation. It may be reduced by distraction techniques such as using a stethoscope to palpate the abdomen, and by administering analgesics. *Rigidity* is the involuntary contraction of abdominal wall muscles that resolves only after anesthesia. "*Rebound tenderness*" is worsening abdominal pain following sudden release of pressure of the palpating hand. It indicates peritoneal irritation. *Rebound tenderness* may also be elicited by abdominal percussion, patient coughing or jolting the bed, or having the standing patient rock back on his heels [4]. Examination techniques eliciting characteristic responses as well as classic sites for referred pain will be discussed under the sections on individual abdominal pathologies.

Evaluation of Patients with Abdominal Pathology

History

Careful history and examination is crucial in diagnosing abdominal pathology. Initial history and examination should be focused to rule out life-threatening causes, which if found, mandates immediate specialist consultation for corrective action. The principal symptoms of abdominal pathology are abdominal pain, nausea, vomiting, diarrhea or constipation, hematemesis/melena, dysuria/hematuria, abdominal distention, anorexia, weight loss, menstrual irregularities, and jaundice. Fever reflects inflammatory/infective states. Characteristics of abdominal pain that need to be elicited in history include duration, nature (colicky, persistent, burning, sharp), location, onset, intensity, radiation, migration, and provoking/relieving factors. Nausea and vomiting may follow vagal response to pain, peritoneal irritation, toxemia, or abdominal distention. Feeding often precipitates pain and emesis. Repeated retching or gastroduodenal irritation/ulceration may produce hematemesis or melena (passage of black, smelly, sticky, slimy stool). Diarrhea is a feature of irritation (infection/inflammation) involving the small or large bowel; constipation may indicate mechanical bowel obstruction or ileus. Anorexia usually accompanies significant abdominal pathology. Urinary symptoms (oliguria, dysuria, frequency, hesitancy, urgency, and hematuria) indicate genitourinary pathology. Jaundice denotes hepatobiliary or pancreatic involvement [2, 3]. Fever reflects inflammatory/infective states. Back pain may indicate retroperitoneal organ involvement (renal colic, pyelonephritis, abdominal aortic aneurysm).

History of trauma, especially prior surgery, is significant. Postoperative adhesions cause over three-fourths of all episodes of bowel obstruction. Embolism from a mural thrombus associated with atrial fibrillation and low flow states secondary to congestive heart failure may cause mesenteric ischemia and bowel infarction. Diabetic ketoacidosis (edema of the mesentery), sickle cell crises (infarction of liver, spleen, or kidney), acute intermittent porphyria (possible visceral ischemia), and renal insufficiency may all cause abdominal pain, confirming the association with cardiorespiratory and systemic illnesses [2, 5].

History of amenorrhea in women of childbearing age may indicate pregnancy. Many features of abdominal pathology (nausea, vomiting, constipation, dysuria, pelvic/abdominal discomfort) are characteristics of normal pregnancy. Medications (antiarrhythmics, nonsteroidal anti-inflammatory agents – NSAIDs, steroids, beta-blockers, anticoagulants, and over-the-counter medications and supplements) often contribute

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to abdominal crises and interfere with assessment by causing abdominal pain, bleeding, arrhythmias, bradycardia, and hypotension. Alcohol and recreational drug use/abuse also promote or worsen abdominal pathology [6]. In evaluating infants and young children, history is obtained from the parent or caregiver; older children often provide a coherent history, though clarification should be sought from the caregiver. Menstrual and sexual histories are important in adolescents and older age-groups [7].

Abdominal pathology in elderly patients is more difficult to evaluate. Cognitive impairment and poor pain perception complicate assessment of pain. Increased intestinal transit time predisposes to constipation and ileus. Immunosenescence of B and T cells result in inadequate febrile and leukocytic response, increasing risk of infections. Decreased renal function delays clearance of medications. Chronic diseases and prior abdominal surgery, more frequent in older people, also impact pain perception and disease progression. Elderly patients are usually on multiple medications (beta-blockers, NSAIDs, anticoagulants, narcotics, antidepressants) all of which alter perception and progression of abdominal pathology, and influence its prognosis [6, 8].

Physical Examination

Presence of shock (hemodynamic compromise) suggests systemic sepsis, significant intra-abdominal bleeding or peritonitis. Signs of trauma (closed head injury, chest, pelvis, long bones) should be identified. Cardiorespiratory, pelvic/rectal examination, and examination of the back complement abdominal examination in evaluating the acute abdomen.

A systematic approach (inspection, auscultation, palpation, and percussion) is recommended. All hernial orifices (umbilical, inguinal femoral) and abdominal incisions should be palpated for masses (possible hernia). Presence of guarding, rigidity and rebound tenderness on abdominal palpation suggests ischemic bowel or peritonitis. Recent increase in size, tenseness, tenderness, or absent cough impulse over a hernia suggests ischemia of contents (entrapped bowel or omentum). Re-examination enables the provider to detect evolving pathology. Organ-specific palpatory signs consistent with specific pathology (Murphy's sign in cholecystitis or Rovsing's sign in appendicitis) may be present. Percussion is useful in detecting free fluid, gaseous distention, and rebound tenderness. Auscultation detects abnormal bruits and borborygmi (peristaltic sounds); hyperactive bowel sounds indicate mechanical bowel obstruction, whereas decreased or absent sounds denote adynamic ileus.

Peritoneal signs are often absent in pregnancy. Lifting and stretching of the abdominal wall prevents underlying inflamed organs from abutting and involving the parietal peritoneum, minimizing guarding. In the later stages of pregnancy, women should be examined in the lateral decubitus position to palpate organs obscured by the gravid uterus. In recumbent patients, the right hip should be elevated slightly in the later stages of pregnancy to avoid compressing the inferior vena cava, which may produce supine hypotension syndrome [9].

Additional Testing: Laboratory Tests

Initial tests include a complete blood count, urinalysis, and analysis of liver and kidney functions. Other specific tests reflecting inflammation/change in organ function are useful in disorders of the pancreas, and in ischemic bowel. Most acute abdominal pathology initiates an inflammatory response and also impacts the function of the involved viscera, which is reflected in changes in body fluid composition. Patient symptoms (gastrointestinal bleeding, vomiting, diarrhea, or hematuria) also influence laboratory values. Some changes seen in acute abdominal pathology include anemia (bleeding), leukocytosis (inflammatory response), hematuria, pyuria, bacteriuria (urinary tract infection, renal trauma), elevation of blood urea nitrogen (BUN) and creatinine (dehydration, poor renal perfusion), elevation of bilirubin and liver enzymes (hemolysis, poor hepatic perfusion, biliary obstruction), elevation of amylase and lipase (pancreatic inflammation), and increased lactic acid (hypotension and shock,

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bowel ischemia and gangrene). Women of child-bearing age should have a pregnancy test. Cardiorespiratory pathology (pneumonia, pulmonary embolism, myocardial ischemia) presenting with abdominal symptoms need to be ruled out by thoracic imaging, measuring cardiac biomarkers, or D-dimer levels.

Age, pregnant state, medications, and pre-existing disease states can affect laboratory values and their utility in diagnosis. The white cell count and alkaline phosphatase may be elevated during normal pregnancy; fever and leukocytosis may be absent in acute abdomen in the elderly [8, 9].

Additional Testing: Imaging

Ultrasonography (US) is useful in suspected pathology of the gall bladder, spleen, and pelvic organs (diagnosis of cholelithiasis and its complications, splenic trauma, ectopic gestation, pelvic inflammatory disease) – Table 1 [10]. It is also recommended in children and in pregnant women. Computed tomography (CT) has greater sensitivity and specificity for bowel (diverticulitis, appendicitis), pancreatic and retroperitoneal (kidney and abdominal aorta) pathology, and is the imaging modality of choice in suspected bowel ischemia. Magnetic resonance imaging (MRI) is useful in patients with iodine allergy or renal dysfunction, and in pregnant women. Other special and focused diagnostic tests are outlined in Table 2 [11, 12]. FAST (focused abdominal sonography in trauma) or E-FAST (extended focused abdominal sonography in trauma) and EMBU (emergency bed-side ultrasound) are both rapid, reliable, performed bedside, and do not interfere with continued resuscitation.

Limited radiation exposure (<5 rad) during pregnancy is safe; greatest fetal risk is between 8 and 15 weeks gestation. Most imaging studies in this generally young and healthy subset involves exposure well below this threshold. If considered necessary, the abdomen should be shielded during diagnostic imaging in pregnancy and patients should be counseled on risk of miscarriage, genetic disease, congenital anomalies, and growth restriction. Both US and MRI are safe during pregnancy [13].

Children are more radiosensitive and have more opportunities to develop radiation-induced cancers (estimated as 1.5–2% of all cancers in the United States) [7]. Hence radiation exposure should be selective and minimized in this age-group.

Preparing the Patient for Surgery

Preoperative Testing

Once the diagnosis and/or the decision to operate is made, further preoperative testing should be based on the need to clarify and optimize the

Table 1 Recommended imaging studies based on location of acute abdominal pain/organ

Epigastrium	Acute abdominal series [a] (erect chest, erect and supine abdominal x-rays), CT (stomach, pancreas)
Right upper quadrant	US+, CT [b] (liver, gall bladder, hepatic flexure)
Left upper quadrant	US, CT (spleen, splenic flexure, pancreas)
Umbilicus	US, CT (pancreas, abdominal aorta, transverse colon)
Right/left lumbar	US/CT (kidney, ascending/descending colon)
Right iliac fossa	US/CT (cecum, appendix, right tube and ovary)
Left iliac fossa	US/CT (sigmoid colon, left tube and ovary)
Hypogastrium	US/CT (urinary bladder, uterus, prostate, seminal vesicles)
External genitalia (males)	US (testes, appendages)

Text from Ref. [10]
+ Ultrasonography
[a]Plain x-rays useful in detecting bowel perforation (free peritoneal air), bowel obstruction (distended bowel, air-fluid levels), and ischemic bowel (pneumatosis intestinalis)
[b]Computed tomography – using oral/rectal and intravenous contrast

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Table 2 Special diagnostic studies in patients presenting with an acute abdomen

FAST/E-FAST	Rapid, reliable, performed bedside in unstable patients. In suspected trauma to solid organs, mesentery. AAA leak
Angiography	Mesenteric ischemia, vascular abdominal emergencies (AAA leak), solid organ trauma (diagnostic and therapeutic embolization)
DPL	Bedside in unstable patients. Saline infused into peritoneal cavity and return analyzed for bowel contents, bile, blood and pus cells. Useful in detecting intraperitoneal bleeding, perforation, peritonitis
Magnetic resonance imaging	If CT contraindicated (iodine allergy, poor renal function). Useful in pregnancy
Helical (spiral) CT	Suspected pulmonary embolism, abdominal trauma
Saline/air/barium enema	In diagnosis and non-operative reduction of intussusception
Non-stress test	Detects fetal well-being. Useful in decision making regarding delivery at later stages of pregnancy at time of laparotomy

Text from Refs. [7, 9, 11]
AAA abdominal aortic aneurysm, *CT* computed tomography, *DPL* diagnostic peritoneal lavage, *FAST* focused assessment with sonography in trauma

patient's physical status and monitor resuscitation and recovery. Patients who have been evaluated and determined to have no preoperative indication for laboratory testing can safely undergo surgery with tests ordered only as needed during or after surgery. Tests should be ordered only when the initial assessment would have indicated a need even if surgery had not been planned.

Resuscitation

Resuscitation commences with assessment and optimization of airway, breathing and circulation, and should precede diagnostic imaging. Cerebral hypoperfusion and mental status changes increase risk of aspiration. Pallor, cyanosis, mottling, prostration, hypotension, tachycardia, and confusion suggest sepsis and dehydration, or ongoing bleeding. Multiple studies have shown that early administration of analgesics does not interfere with subsequent ability to diagnose and treat acute abdominal pathology, nor does it impact patient outcomes [2]. Antibiotics are not administered in stable and immunocompetent patients unless an infective source is evident or identified; immunocompromised patients require early and preoperative broad-spectrum antibiotic administration [11]. Fluid and electrolyte imbalances due to vomiting and third-space sequestration should be corrected, any hypotension reversed, renal perfusion optimized and adequate urine output ensured prior to operative intervention, unless emergent surgery is mandated for continued bleeding or progressing sepsis. It is important to recognize ongoing transfusion requirements, identify and treat life-threatening causes of abdominal pain and monitor patients closely until recovery.

Perioperative Glucose Control

Patients with diabetes mellitus have poorer surgical outcomes, higher perioperative morbidity (coronary events, renal failure, infections), and longer postoperative hospital stays [14]. In critically ill patients requiring intensive care, a lower glycemic target (80–110 mg/dL) is recommended; a fasting glucose under 110 mg/dL and a random glucose under 180 mg/dL are considered desirable in patients less critically ill. Glucose, insulin, and potassium are infused judiciously in the perioperative period to maintain these parameters. Hydration should be maintained and acidosis (ketosis), hypoglycemia, and hypokalemia avoided. Oral agents are withheld on day of surgery. Preoperative medication regime is restored in stable patients in whom oral intake is tolerated. Metformin is usually held for 48–72 h following surgery or contrast-enhanced imaging and restarted after normal renal function is reestablished.

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Laparoscopic Surgery

Evidence-based guidelines recommend laparoscopic surgery in patients with perforated peptic ulcer, acute cholecystitis, acute appendicitis, for adhesiolysis in patients with bowel obstruction caused by adhesions, gynecological disorders, and following abdominal trauma. Diagnostic laparoscopy is useful for assessing peritoneal intactness and avoiding laparotomy in stable patients with penetrating abdominal trauma. It is also valuable in stable patients with blunt abdominal trauma to exclude intra-abdominal injury requiring laporotomy. Laparoscopy results in decreased hospital stay, earlier return of bowel function, less postoperative pain, earlier ambulation, and less incidence of wound infection and incisional hernia. Optimal gestational age at which to perform laparoscopic surgery during pregnancy is unclear, but an upper limit of 26–28 weeks is advocated [13, 15]. Complications include visceral and vascular trauma during entry and dissection, pneumothorax, air embolism, carbon-dioxide narcosis, and low cardiac output.

Etiology of Acute Abdominal Pain in Patients Seeking Emergency Care

Mid-gut volvulus, intestinal atresia, and meconium ileus occur in newborns and infants; intussusception and Meckel's diverticulitis occur in infants and children; appendicitis and acute urogenital pathology are seen in children, adolescents, and young adults (Table 3). Incidence of bowel obstruction, diverticulitis, and consequences of atherosclerosis (aneurysm and bowel ischemia) increase with age [7, 8, 11]. Unusual causes of emergency room visit due to abdominal pain in children include constipation, Henoch-Schonlein purpura, pneumonia, streptococcal tonsillitis (tonsil tummy), gastroenteritis, and functional abdominal pain [7]. Both pregnancy-related causes (miscarriage, ectopic gestation, placental abruption, uterine rupture) and unrelated causes (appendicitis, cholecystitis) may cause acute abdominal pain requiring surgical intervention during pregnancy [13] .

Life-Threatening Causes

Early recognition and management of continued bleeding, bowel ischemia, and infarction minimizes the high associated mortality. History of amenorrhea should be obtained from women of child-bearing age. Myocardial ischemia is a consideration in elderly patients with upper abdominal pain (Table 4).

Abdominal Trauma

Background

Abdominal trauma accounts for over one-eighth of all traumatic injuries. The majority (75%) follow blunt trauma, mainly motor vehicle and auto-pedestrian accidents (50–75%), and direct blows to the abdomen (15%) [16–18]. As blunt injuries

Table 3 Etiology of acute abdominal pain in patients seeking emergency care

In children/adolescents	In adults/elderly
Acute appendicitis/cholecystitis	Acute appendicitis/cholecystitis
Small/large bowel obstruction (intussusception, volvulus, hernia, atresia, meconium ileus)	Small/large bowel obstruction, bowel perforation
Ectopic gestation	Acute pancreatitis
Twisted ovarian cyst, testicular torsion	Diverticulitis
Renal/ureteric colic	Mesenteric vascular occlusion
Pelvic inflammatory disease	Ischemic colitis
Meckel's diverticulitis	Renal/ureteric colic
	Ectopic gestation

Text from Refs. [7, 9, 11]

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Table 4 Life-threatening causes of abdominal pain

Cause	Features
Ruptured abdominal aortic aneurysm	Hypotension, pulsatile abdominal mass, abdominal/low back pain. CT diagnostic
Rupture liver/spleen	Secondary to trauma, mononucleosis, rarely malaria, hematologic conditions. Abdominal pain, hypotension
Ruptured ectopic pregnancy	Amenorrhea, lower abdominal pain, hypotension
Hollow viscus perforation	Sudden severe initially localized then spreading abdominal pain, vomiting, abdominal distention, possible history of trauma including surgery and endoscopy
Intestinal ischemia/ infarction	History of CAD, atrial fibrillation. Sudden severe abdominal pain out of proportion to physical findings, hypotension, prostration
Myocardial infarction	Upper abdominal pain, tachycardia, hypotension, minimal abdominal findings

Text from multiple sources

usually involve multiple viscera within and outside the abdomen and pose diagnostic challenges, they have a higher mortality compared with penetrating injuries [18]. Abdominal organs are especially vulnerable to lower chest wall, back, buttock, or pelvic trauma. The spleen, followed by the liver, is the most common solid organ involved; the bowel is the most common hollow viscus injured. Penetrating injuries usually involve the bowel and liver. Stab wounds to the abdomen are three times more common than gunshot wounds, though gunshot wounds account for almost all (90%) mortality due to penetrating injuries.

Abdominal trauma, also the second leading cause of death among physically abused children, accounts for nearly 10% of children admitted to pediatric trauma centers; most (85%) follow blunt abdominal trauma (BAT). Children under 2 years of age are at greatest risk of abuse [17, 19]. The thin abdominal wall in children and larger proportional size of solid organs compared with adults place them at higher risk for abdominal injuries after BAT. The liver, spleen, and kidney followed by the gastrointestinal tract are most commonly traumatized in children [17].

Diagnosis

Patients with BAT may pose a complex diagnostic challenge. Nearly half of patients may have no localizing features on admission. History may not always be available due to associated injuries, lack of witnesses, altered mental status, and drug and alcohol use. Physical examination should encompass whole body evaluation including the cranium and cervical spine, chest, abdomen, pelvis and long bones. In penetrating injuries, entry and exit wounds should be carefully assessed as they predict nature and extent of injury. Hypotension, most often caused by solid viscus or vascular injury has high specificity for abdominal trauma [18, 20]. Abdominal distention, guarding, rebound tenderness and rigidity, presence of a seat-belt sign, and concomitant femoral fracture also have high specificity for intra-abdominal injuries [20]. However, physical examination has low sensitivity (55–65%) in BAT [17].

Management

Initial management should optimize patient's airway, breathing, and circulation. Laboratory analysis should focus on evaluating patient's clinical status and stability, and the need to detect and correct ongoing bleeding, fluid, electrolyte and acid–base imbalance, and renal and tissue hypoperfusion. Serial measurements help direct resuscitative efforts and monitor patient response. A complete blood count, urinalysis, a comprehensive metabolic panel (evaluating liver and kidney function), serum amylase and arterial blood gases are obtained initially. Patient is also typed and cross-matched as preparation for possible packed cell transfusions. Acidosis, hematuria, and anemia have high specificities for intra-

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abdominal injury [20]. Adequate intravenous access (two large-bore peripheral lines or a central line) is obtained, a nasogastric tube is inserted to decompress the proximal bowel and a Foley catheter is placed to monitor urine output.

In hemodynamically unstable patients (systolic blood pressure $\leq$ 90 mmHg) with BAT, bedside ultrasound (FAST –focused assessment with sonography in trauma or E-FAST- extended focused assessment with sonography in trauma), when available, should be the initial diagnostic modality performed to identify the need for emergent laparotomy [16, 21]. FAST has lower sensitivity (79%) but higher specificity (95%) for BAT. FAST is quick, performed bedside, identifies the presence of free fluid but not its etiology or the injury, and may be absent when performed early before enough fluid (400 mL) accumulates. Accuracy of FAST is extremely operator-dependent [16, 21].

Diagnostic peritoneal lavage (DPL) involves introducing an infra-umbilical catheter by an open, semi-open, or closed technique under local anesthesia with or without conscious sedation, after decompressing the stomach and urinary bladder [22]. Aspiration of 10 mL of blood is considered positive. If none is aspirated, 1 L of normal saline or lactated Ringer's solution is infused into the peritoneal cavity, allowed to drain out and examined for red blood cells ($>$100,000/mm^3 considered positive), white blood cells ($>$500/mm^3 considered positive), amylase, bile, food particles, and bacteria [22]. The presence of lavage fluid in an intercostal chest tube or Foley catheter is also documented (suggesting diaphragmatic or bladder rupture). DPL is useful in both blunt and penetrating injuries in patients with altered mental status or hemodynamic instability when FAST is not available. It is also indicated in patients with significant trauma to other systems (thorax, cranium, pelvis, long bones) requiring surgical intervention with equivocal abdominal findings. DPL does not identify the source of bleed, or retroperitoneal injuries. Prior abdominal surgery, obesity, hepatic cirrhosis, pregnancy, and coagulopathy are contraindications. DPL has largely been superseded by FAST in unstable patients and by helical CT in stable patients.

Helical CT has both high sensitivity and specificity (97–99%) for intra-abdominal injury though less than one-fifth of CTs are positive for trauma and fewer patients (3%) end up requiring surgery [20]. CT is expensive, time-consuming, needs expertise for interpretation, and involves infusion of contrast and radiation, with risks of contrast-induced nephropathy and radiation-induced cancer. Clinical prediction rules have been developed to minimize its use and optimize its value. One rule consisting of seven variables (hypotension, Glasgow coma scale $<$14, costal margin tenderness, abdominal tenderness, femur fracture, hematuria $\geq$25 RBC/hpf, hematocrit $<$30 and chest x-ray showing rib fracture or pneumothorax) has high sensitivity; patients without any of these variables have negligible risk of intra-abdominal injury and are unlikely to benefit from abdominal CT scans [23]. CT may be performed with only intravenous contrast; ingesting oral contrast is unnecessary even when bowel injury is a concern [16].

Intravenous pyelography and cystourethrography are of value when damage to the urinary tract is suspected by the presence of lower abdominal, retroperitoneal or perineal trauma, hematuria or urinary retention. Laparoscopy is most useful for assessing penetrating injuries to the thoracoabdominal region in stable patients (especially the diaphragm). It has little value in BAT, assessing hollow viscus or retroperitoneal injuries, or evaluating the extent of injury to solid organs like the liver or spleen [18].

Surgery involves laparotomy, identifying the injury, staunching bleeding sources, repairing rents in hollow or solid viscera, excising organs injured beyond repair (spleen, kidney, bowel segments), peritoneal washout, and closing the incision either primarily or secondarily based on the degree of wound contamination and need for re-exploration. Resuscitation with fluids, packed cells, and blood products are continued. Invasive monitoring and ventilation in an intensive care unit may be necessary in critically ill patients until recovery.

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Appendicitis

Background

Inflammation of the appendix follows luminal obstruction by fecoliths, Peyer's patches, foreign bodies, worms, and rarely tumors (carcinoid, carcinoma). The resultant rising intraluminal pressure causes distention, ischemia, and perforation. The parietal peritoneum, surrounding bowel and omentum attempt to localize the infection, on occasion, forming an appendicular mass. Perforation is more common among patients at extremes of age and in pregnant women.

Over 250,000 cases of appendicitis are diagnosed annually; the peak incidence occurs in the second decade of life (median age at diagnosis – 10–11 years) [24]. There is a slight male predominance (1.4:1). Appendicitis is also the most common non-obstetric surgical emergency during pregnancy.

Diagnosis: History and Examination

Classic symptoms of appendicitis (seen in <50% of children) include dull periumbilical pain migrating to the right lower abdomen, nausea, vomiting, anorexia, and low-grade fever [24]. Urinary frequency and urgency, diarrhea, and tenesmus are more common in pelvic appendicitis. In adults, right lower abdominal pain and migration of pain best predict appendicitis; absence of fever or pain before vomiting greatly reduces its likelihood. Pain may shift to the right lumbar area and even to the right upper quadrant of the abdomen in the later stages of pregnancy.

Guarding and tenderness in the right lower abdomen (McBurney's sign – most specific), and rebound tenderness (elicited on palpation/percussion) predict appendicitis. The inflamed appendix causes spasm of the adjacent abdominal wall and retroperitoneal musculotendinous structures resulting in overlying rigidity, and pain on ipsilateral hip hyperextension or internal rotation (psoas sign, obturator sign). Increase in intra-abdominal pressure as in coughing reproduces pain (Dunphy's sign). Palpation of the left iliac fossa shifts the bowel and intracolonic air producing greater pressure over the inflamed appendix, worsening the pain (Rovsing's sign) as does dropping from tiptoe to heel with a jarring landing (Markle sign- jar tenderness). Vomiting, rectal tenderness, rebound tenderness, and fever have greater positive predictive value in children than in adults, whereas right lower quadrant tenderness is less helpful [24–26].

Diagnosis: Investigations

Leukocytosis with a left shift and an elevated C-reactive protein (CRP) characterize appendicitis. Ultrasound shows appendiceal thickening, periappendiceal edema, increased peritoneal fluid, hypervascularity (on Doppler US), and the "sonographic McBurney's sign" – tenderness in response to pressure from the US probe. CT also shows the enlarged and thickened appendix and periappendiceal stranding. If both guarding and leukocytosis (>10,000/mm^3) are present – probability of appendicitis is high (>90%); elevated white count and C-reactive protein also increases likelihood of appendicitis (~90%). CT has high sensitivity and specificity (>90%) for appendicitis. US with graded compression has slightly lower sensitivity (85–90%) but high specificity (>90%). Initial US, followed by CT in patients with ambiguous findings on US, minimize radiation; preferred in children [7, 11, 26, 27].

Scoring systems (Alvarado, Pediatric appendicitis and Ohmann scores) incorporate several features in history, examination and laboratory tests to predict likelihood of disease. Knowledge of the pretest probability is important to maximize utility of scoring systems. When pretest probability is low, a higher score is required to rule in the diagnosis. Patients with a high likelihood of appendicitis should undergo appendectomy; those with a low probability should be discharged or treated for other pathology; those with an intermediate probability should be imaged, and based on the information, should undergo surgery, or observation until the clinical picture becomes clearer [28].

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Appendicitis: Differential Diagnosis

Inflammatory, ischemic or other pathology in the right lower abdomen (Cecal diverticulitis, ectopic gestation, mesenteric adenitis, pyelonephritis, ureteric calculus, terminal ileitis) may all mimic appendicitis.

Appendicitis: Treatment

Appendectomy is usually performed through a low transverse (Lanz) or the classic McBurney muscle-splitting incision. Laparoscopic appendectomy is safer and causes fewer complications; these patients have shorter postoperative stays and return to work earlier.

Antibiotic choices in appendicitis include piperacillin-tazobactam and cefoxitin, which are effective against the *E.coli*, *streptococcus* species, *anerobes,* and *pseudomonas*, commonly found in appendicitis. Antibiotics are continued until features of infection resolve [24]. Whereas, a single-dose is sufficient in uncomplicated appendicitis, longer (5–7 day) courses are indicated in perforated appendicitis [24].

Wound infection, the most common complication, is minimized by intraoperative peritoneal lavage, which reduces bacterial contamination. Intra-abdominal collections (pelvic, subphrenic, right paracolic gutter) are rare, could follow ruptured appendicitis, and may need open or imaging-guided drainage. Urinary retention, urinary tract infections, and pneumonia are more common in the elderly, the debilitated and the immunosuppressed. Involvement of the fallopian tubes in the inflammatory mass may cause infertility. Appendicitis during pregnancy may cause miscarriage or preterm labor.

Patients presenting late (after 72 h, with localized infection, appendicular mass on examination or on imaging, absent systemic sepsis and peritonitis) may be managed nonoperatively with broad-spectrum antibiotics and image-guided drainage of fluid collections. Those with appendicoliths appear to have a higher likelihood of recurrent infections and merit consideration for interval appendectomy [24].

Cholelithiasis and Cholecystitis

Background

Cholelithiasis is a significant problem among adults and the elderly in the United States (6.3 million men, 14.2 million women aged 20–74 years) [29]. The female predominance persists across ethnicities (non-Hispanic whites, African-Americans and Mexican-Americans), and is five-fold among 20–29 year olds, though less among older age groups. The highest incidence of cholelithiasis appears to be among North American Indians over 30 years (nearly three-fourths). Gallstones are also associated with obesity (sevenfold increase in obese women), physical inactivity, parity, rapid weight loss, tobacco use, diabetes mellitus, lower alcohol consumption, and lower serum cholesterol [29, 30]. Other contributing factors and associations include Crohn's disease, ileal resection, medications (ceftriaxone, clofibrate, estrogens, octreotide, steroids), spinal cord injuries, and total parenteral nutrition [31].

Pathophysiology

Gallstones develop as a result of precipitation of cholesterol and calcium salts in supersaturated bile [32]. In addition, impaired gall bladder motility, increased biliary nucleation, presence of excess pronucleating proteins, and increased mucin production appear to promote gallstone formation [33]. Gallstones are classified as either cholesterol stones (commonest, nearly 80%) or pigment stones (usually associated with hemolytic disorders – hereditary spherocytosis, sickle cell disease). Black pigment stones containing calcium bilirubinate, form in sterile bile and are rare below 50 years of age; brown pigment stones are formed in the bile ducts and result from chronic bacterial or parasitic infection [33]. Though the majority (80%) of patients with gallstones are asymptomatic (silent gallstones), the rest present with symptoms and complications necessitating intervention.

Gallstones may cause functional dyspepsia, biliary colic, acute cholecystitis, mucocele of the

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gallbladder, gallbladder perforation and biliary peritonitis, choledocholithiasis, obstructive jaundice, cholangitis, acute and chronic pancreatitis, and gall stone ileus. Acute cholecystitis is inflammation of the gallbladder wall most often (90%) following cystic duct obstruction due to gallstones or biliary sludge; it develops in 1–3% of patients with gallstones [30, 32]. Following cystic duct obstruction, continued mucus production causes gallbladder distention, ischemia, and release of inflammatory mediators, necrosis, and perforation, either at the neck or the fundus that has the least blood supply, leading to biliary peritonitis. Secondary polymicrobial infection (*gram-negative bacilli*, *anerobes*, *enterococci*) may complicate cholecystitis and overgrowth of gas-forming bacteria (*clostridium species, E.coli*) within the gallbladder leads to emphysematous cholecystitis.

Diagnosis: History and Examination

Acute cholecystitis has a female preponderance (threefold) and presents with a rapid onset of severe, cramping right upper abdominal (RUQ) pain initially radiating to the back, then localizing to the RUQ. Abdominal pain lasting over 6 h indicates cholecystitis and not biliary colic [31]. Low-grade fever, chills, malaise, nausea, vomiting, and anorexia coexist [30, 32]. Almost three-fourths of patients report prior episodes of biliary colic. Occasionally the pain may localize in the chest or back [31]. Though vomiting and poor oral intake may lead to oliguria and high-colored urine, orange-colored urine, and clay-colored stools suggest complete biliary obstruction due to choledocholithiasis or pancreatobiliary tumors. Mirizzi syndrome refers to a gallstone impacted in the gallbladder neck or cystic duct compressing the common hepatic duct, causing varying degrees of biliary obstruction and jaundice. Elderly and immunocompromised patients may have milder symptoms.

Physical findings include low-grade fever (high fevers suggest gangrene or perforation), tachycardia, scleral icterus (more common in the elderly), and RUQ guarding and tenderness [31]. Murphy's sign (cessation of inspiration in response to pain on RUQ palpation) is characteristic of cholecystitis, has high sensitivity (97.2%), though less reliable in the elderly [34]. The gallbladder may be palpable in up to 33% of patients, especially those with first episodes [31]. Hypotension and mental status changes suggest sepsis, more commonly in the elderly, the debilitated and the immunosuppressed.

Diagnosis: Investigations

No solitary or combination of laboratory abnormalities is sufficiently sensitive or specific for cholecystitis. Leukocytosis with bandemia, and elevations of serum bilirubin and liver enzymes are observed, though serum bilirubin levels over 4 mg/dL or elevated amylase and lipase suggest choledocholithiasis [31].

Abdominal radiographs may rarely show gallstones or biliary air and seldom help diagnose cholecystitis, but may exclude other conditions such as bowel obstruction or perforation. US is both sensitive (82%) and specific (81%) for cholecystitis. Sonographic Murphy's sign (RUQ tenderness induced by the US probe) has a positive predictive value over 90% in detecting acute calculous cholecystitis. Presence of pericholecystic fluid and gallbladder wall thickening over 4 mm on US are other findings suggesting acute cholecystitis [31]. MRI has comparable sensitivity (86%) and specificity (82%) [35]. CT is less sensitive (75%) than US, has higher specificity (93%) and is more useful for identifying other abdominal (especially solid organ) pathology, and in detecting emphysematous cholecystitis, abscess, gallbladder perforation, and peritonitis. CT and MRI findings in cholecystitis are the same as that in US. HIDA (hepatobiliary iminodiacetic acid) scan, performed after injecting technetium-labeled derivatives of iminodiacetic acid, usually visualizes the gallbladder in 30 min and the small bowel in 60 min. Non-filling of the gallbladder within 60 min in patient with acute upper abdominal pain is highly suggestive of acute cholecystitis. HIDA scan has the highest diagnostic accuracy of all imaging modalities in detecting acute cholecystitis (sensitivity 96%, specificity 90%) [35] .

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Differential Diagnosis

This includes other inflammatory intra-abdominal or pulmonary pathologies (peptic ulcer disease, pancreatitis, appendicitis, renal colic, pyelonephritis, pneumonia, liver abscess, liver tumors, and gonococcal perihepatitis) [31]. Most of these can be ruled in or out by a combination of clinical assessment, laboratory analysis and imaging.

Cholecystitis: Treatment

Treatment involves hospital admission, intravenous hydration, bowel rest, pain relief, and intravenous broad-spectrum antibiotics (ampicillin and gentamicin, ampicillin-sulbactam, piperacillin – tazobactam, a third-generation cephalosporin such as ceftriaxone, or a fluoroquinolone such as levofloxacin) [32]. Early cholecystectomy (within 24–48 h) is recommended. Earlier cholecystectomy within 12–24 h is a consideration in older patients, diabetics, and the immunosuppressed, more prone to develop rapid disease progression and complications (gangrene, emphysematous cholecystitis, empyema, or rupture) [32]. Early cholecystectomy is safe, highly successful, feasible with the laparoscope, has a low conversion rate to the open procedure, and associated with decreased hospital stay and earlier return to usual activities [30]. Delayed cholecystectomy (4–8 weeks after the acute episode) is not recommended as it does not reduce morbidity or conversion to open cholecystectomy, and increases risk of recurrent cholecystitis in the interim [30]. Ailing patients with comorbidities, who are poor surgical candidates, benefit from antibiotics and supportive care, and a percutaneous cholecystostomy under US or CT guidance.

Laparoscopic cholecystectomy is the gold standard for uncomplicated acute cholecystitis. Open cholecystectomy is preferred in patients with complications such as pancreatitis, gallbladder perforation and peritonitis, sepsis, suspected gallbladder cancer, or cholecystoenteric fistulas. Emergency surgery, dependent functional status, male gender, worsening American Society of Anesthesiology (ASA) class (3 through 5), older age, and presence of comorbidities or laboratory abnormalities (ascites, bleeding diathesis, pneumonia, decreased serum sodium or albumin, elevated white count, BUN, alkaline phosphatase or international normalized ratio (INR)) are all predictive of an initial decision to perform open cholecystectomy or a greater rate of conversion to the open procedure[36].

Acalculous Cholecystitis

Acalculous cholecystitis usually follows major trauma or surgery, resuscitation from cardiac arrest, systemic sepsis or presence of major comorbidities such as congestive heart failure, end-stage renal disease, and cancer [37]. Delayed diagnosis, poor patient status, and increased complication rate (gangrene, perforation, and peritonitis) associated with acalculous cholecystitis escalate mortality (around 30%). Bile stasis, gallbladder ischemia, and release of multiple vasoactive and inflammatory mediators are responsible for the cellular hypoxia and mucosal injury initiating this process. Unreliable clinical features, paucity of physical signs and confusing laboratory findings, make early diagnosis a challenge. US is diagnostic – features include wall thickness $\geq$ 3.5 mm (sensitivity 80%, specificity 98.5%), gallbladder distention, sonographic Murphy sign, pericholecystic fluid, intramural gas and a "halo" indicating intramural edema. CT is more accurate (sensitivity and specificity 95%); findings parallel that on US. HIDA scan is marginally less accurate than CT (sensitivity 80–90%, specificity 90–100%) [38]. Treatment includes intravenous hydration, bowel rest, broad-spectrum antibiotics as in calculous cholecystitis, and continued treatment of the primary pathology precipitating this event. Cholecystectomy (laparoscopic or open) is curative; percutaneous cholecystostomy controls the infection in most (85–90%) patients [37].

Special Situations

Conservative management of acute cholecystitis is recommended in pregnancy unless pancreatitis, ascending cholangitis, or common bile duct

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obstruction develops. Surgery is indicated in treatment failure. Laparoscopic cholecystectomy is the most common laparoscopic procedure during pregnancy, ideally performed in the second trimester [13].

Nearly a third of elderly patients with cholecystitis present with minimal abdominal pain and peritoneal signs, not correlating with severity of infection. Empyema of the gallbladder, gangrenous cholecystitis, biliary peritonitis, subphrenic or hepatic abscess may all occur in the elderly with minimal symptoms, little fever or elevated white counts. Emphysematous cholecystitis due to gas-producing organisms is also more common among the elderly, especially in men and diabetics [8].

Oral Dissolution of Cholelithiasis

This is an option in symptomatic patients with small ($\leq$5 mm) cholesterol stones in a functioning gallbladder and a patent cystic duct ($<$10% of cholesterol stones), who are unfit for surgery [39]. Options include chenodeoxycholic acid and ursodeoxycholic acid administered for 6–12 months. Recurrence is seen in nearly 50% of patients with multiple gallstones. Oral dissolution combined with lithotripsy is another treatment option avoiding open cholecystectomy but may also involve endoscopic sphincterotomy and removal of stones from the common bile duct and, in many cases, subsequent open cholecystectomy.

Inguinal Hernia

Background

A hernia is a protrusion of a viscus or tissue through an anatomical opening or an abnormal weakness in the wall of its containing cavity. Abdominal wall hernias develop in one in 20 patients; inguinal hernias constitute the majority (75%) [40]. Other commonly occurring hernias include umbilical, paraumbilical, and incisional hernias; the rest (femoral, epigastric, spigelian, lumbar, gluteal, sciatic hernias) are uncommon. Multiple causes predispose to the development of hernias either by increasing intra-abdominal pressure or stretching and weakening of the abdominal wall (ascites, aging, chronic cough, constipation, heavy lifting, obesity, obstructive uropathy, pregnancy, prior lower abdominal surgery, smoking, and weight loss). Existence of an anatomical defect (inguinal canal, umbilicus, femoral canal) also predisposes to its development [40–42]. Inguinal hernias have a male predominance and are more common on the right.

Hernia- Anatomy

A hernia comprises of the hernial sac, the coverings of the sac and its contents. The "neck" of the sac is the narrow area usually located at its junction with the peritoneal cavity. The hernia contents can be diverse – extraperitoneal fat or omentum (omentocele), intestinal loops (enterocele), bladder diverticulum, or ovary and fallopian tube. The composition and types of hernia are outlined in Table 5.

The superficial inguinal ring is an opening in the external oblique aponeurosis just above and lateral to the pubic tubercle. The deep inguinal ring is a defect in the transversalis fascia just above the mid-point of the inguinal ligament. The inguinal canal traverses the two rings and contains the spermatic cord in men (round ligament in women), the ilioinguinal nerve, and the genital branch of the genitofemoral nerve. The inguinal canal is bounded anteriorly by the external oblique aponeurosis, posteriorly by the transversalis fascia, inferiorly by the inguinal ligament, and superiorly by the arched fibers of the conjoint tendon. Whereas in infants, the two rings are adjacent and the canal is short; in adults, the canal is oblique, directed downwards and medially, running from deep to superficial. Hesselbach's triangle, which forms the floor of the inguinal canal, is bounded superiorly and laterally by the inferior epigastric vessels, medially by the rectus sheath and inferiorly by the inguinal and pectineal ligaments [40].

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Table 5 Types of hernia

Type	Nature
Reducible hernia	Hernial contents can be reduced into the peritoneal cavity usually be the patient or the surgeon (taxis). Omentum has a doughy consistency and is difficult to reduce. Bowel loops reduce with a gurgle
Irreducible hernia	Inability to reduce hernial contents-usually due to adhesions between sac and contents or between contents. Predisposes to obstruction and strangulation. Attempts at reduction may reduce the sac with its contents
Obstructed hernia	Bowel obstruction without features of bowel ischemia
Strangulated hernia	Hernial contents become ischemic and gangrenous. May involve omentum or intestine
Sliding hernia (hernia en glissade)	Type of inguinal hernia in which the posterior wall of the hernia sac is comprised of cecum or sigmoid colon, peritoneum and occasionally a part of the urinary bladder
Richter's hernia	Hernial sac contains only part of the bowel
Littre's hernia	Hernial sac containing a Meckel's diverticulum
Maydl's hernia	Hernial sac contains two loops of intestine with an intraperitoneal central loop that may develop ischemia
Pantaloon hernia	Inguinal hernia with indirect and direct components

Text from multiple sources

Inguinal Hernia: Types, Diagnosis, and Complications

Inguinal hernias pass either through the inguinal canal in their entirety (through the internal to the external ring, lateral to the Hasselbach's triangle – *indirect* – two-thirds of inguinal hernias) or through the weakened floor of the canal, through the Hasselbach's triangle (*direct*). The neck of an indirect hernia is thus lateral to the inferior epigastric vessels, whereas that of a direct hernia is medial [40].

In infants, and children inguinal hernias usually result from a persistent processus vaginalis, present at birth or shortly thereafter. Most children (90%) with cryptorchidism (maldescended testis) have an associated patent processus vaginalis and may present with an asymptomatic, irreducible, or strangulated inguinal hernia. Adults usually have a more insidious presentation, though a rapid onset may be precipitated by unusual straining or exertion. Patients may complain of a pulling sensation, discomfort, pain, or an increasing groin bulge. Occasional soreness or burning along the distribution of the ilioinguinal nerve (scrotum, medial upper thigh) may be noticed. Standing, coughing, and straining makes the hernia more noticeable; hence patients are usually examined in the upright position and asked to cough or strain. The skin over the base of the scrotum can be invaginated to feel the superficial ring (*invagination test*). If the patient is asked to cough, the impulse from an indirect hernia is felt at the tip of the finger, whereas one from a direct hernia is felt at its pulp. The internal ring can be occluded by pressure after reducing the hernia (*internal ring occlusion test*); if the patient is asked to strain, an indirect hernia will remain reduced whereas a direct hernia will pouch. In the *Zieman's* technique, the index, middle, and ring fingers are placed over the deep, superficial, and femoral rings and the patient asked to cough, thereby helping to distinguish indirect and direct, inguinal, and femoral hernias. An omentocele has a doughy consistency; an enterocele gurgles on palpation and attempted reduction, and the initial portion of the reduction is more difficult. Bowel sounds can be heard on auscultation over an enterocele.

Irreducibility is diagnosed when the hernia does not reduce spontaneously in the recumbent position, or on attempts at reduction. Patients with obstructed hernias present with features of bowel obstruction (colicky abdominal pain, vomiting, abdominal distention, and constipation). Absent cough impulse, recent increase in size, a tense and tender swelling, and a tender distended abdomen indicate strangulation of the

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hernial contents (rare – 0.55% of asymptomatic hernias followed over 4 years) [43]. Imaging studies (US, CT) are useful in confirming the diagnosis of hernia and recognizing coexisting problems (cryptorchidism). Abdominal radiographs help diagnose bowel obstruction (distended bowel, air-fluid levels).

Differential Diagnosis

The differential diagnosis includes other inguinoscrotal pathology mimicking a hernia (vaginal hydrocele, spermatocele, undescended testis, an encysted hydrocele or lipoma of the spermatic cord, or a femoral hernia) [44].

Inguinal Hernia: Treatment

Watchful waiting is an option in patients with small hernias and minimal or no symptoms [45]. Most patients, over time, will develop discomfort enough to require surgery. In infants and children, a *herniotomy* – reduction of the hernial contents and ligation of the patent processus vaginalis (hernial sac) at the level of the deep ring – is sufficient. In adults, the posterior wall of the inguinal canal is strengthened either by approximation or imbrication using non-absorbable sutures (*herniorrhaphy*) or by using prosthetic material (*hernioplasty*). The traditional *Bassini* repair involves approximating the conjoint tendon to the inguinal ligament. The *Shouldice* repair involves a more extensive dissection of the inguinal region to define the layers of the abdominal wall and imbricating the posterior wall of the inguinal canal using stainless steel wire or polypropylene. It is considered the best non-mesh technique for inguinal hernia repair (recurrence 3.6%) [46]. In the "Lichtenstein tension-free hernia repair," the posterior wall is reinforced with a polypropylene mesh, placed preperitoneally and sutured in position. This acts as scaffolding in which tissue forms, further buttressing the abdominal wall, and significantly reducing the risk of recurrence (0.8%) [46]. The *plug and patch* technique uses two layers of polypropylene mesh to plug the defect (deep ring or the posterior wall defect) followed by buttressing the posterior wall further with a polypropylene mesh. The mesh may also be placed intra- or extraperitoneally, through laparoscopy. Advantages of laparoscopy include confirming the diagnosis of hernia, visualization of the defect and hernial sac, small incisions, and rapid return to work [41]. Disadvantages include need for general anesthesia and mesh, contributing to increased costs. Antibiotics are not indicated in elective hernia repairs.

Surgical techniques in irreducible and obstructed hernias are no different though patients with bowel obstruction need bowel rest, nasogastric suction, and replacement of fluids and electrolytes, continued until return of bowel function. Strangulated hernias with ischemic contents require resection of the contents (omentum, bowel resection followed by anastomosis); concomitant mesh repair increases risk of infection and rejection.

Complications

Operative complications include hemorrhage, hematoma, wound infection, and injury to the adjacent structures (bowel, bladder, spermatic cord structures, and nerves) and mesh rejection. Attention to detail and meticulous technique minimize complications. Long-term complications include recurrence (least in the Shouldice and mesh repairs), pain, and infertility (injury to the vasa deferentia in bilateral hernia repairs). Over half of patients may experience some degree of pain following surgery; less after the mesh or laparoscopic procedures. Pain may follow injury to the pubic tubercle, spermatic cord, the iliohypogastric or ilioinguinal nerves, or the lateral cutaneous nerve of the thigh. Though pain improves over time, some patients may require trigger point injections, medications, or surgical neurolysis for pain relief. Chronic pain is more common after recurrent hernia repair and in patients experiencing severe pain soon after surgery [41, 47].

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Bowel Obstruction

Background

Intestinal obstruction may be divided into two types – dynamic (mechanical) obstruction of the bowel lumen with continued proximal peristalsis and progressive bowel distention, and adynamic (functional) obstruction with absent or inadequate peristalsis [48]. Obstruction may involve any part of the bowel including the esophagus, stomach, small and large bowel (Table 6). Adhesions, neoplasms, and hernias account for most (>90%) small bowel obstructions, with adhesions accounting for over three-fourths. Malignancy, volvulus, and diverticulitis cause most large bowel obstructions (>80%) [5]. Proximal to the site of obstruction the bowel distends with air (swallowed air, luminal gas) and fluid (impaired absorption, increased secretion) leading to bowel wall edema, loss of fluids and electrolytes, and dehydration [49]. In *closed loop obstruction* (bowel obstructed both proximally and distally due to adhesions or volvulus) the intermediate segment distends rapidly, with initially venous followed by arterial occlusion that progresses rapidly to ischemia, gangrene and perforation, and supervening infection, making it a surgical emergency.

Diagnosis: History and Examination

Symptoms of bowel obstruction depend on the site of the obstruction. Patients with esophageal obstruction may present with dysphagia, odynophagia, retrosternal discomfort or pain, retching, vomiting, regurgitation, and anorexia. Patients with gastric outlet obstruction (GOO) experience upper abdominal discomfort and vomiting, anorexia, and early satiety. Associated gastritis may cause hematemesis. Fetor is common in both esophageal and GOO. Patients with small bowel obstruction (SBO) generally experience pain, vomiting, abdominal distention, and constipation, in that order, whereas those with large bowel obstruction (LBO) experience initial constipation followed by abdominal distention, pain, and vomiting (the exception is in closed loop obstructions such as cecal or sigmoid volvulus, in which patients experience severe colicky followed by persistent abdominal pain out of proportion to physical findings, abdominal distention, and vomiting) [49]. Abdominal pain is usually colicky, though it becomes persistent in the presence of ischemic bowel or peritonitis; frequency and intensity diminishes with prolonged obstruction. The vomitus is usually clear or contains altered blood in GOO, contains bile in high SBO, is yellow in low SBO, and feculent in LBO. Abdominal distention is minimal or absent

Table 6 Site and causes of bowel obstruction

Site of obstruction	Cause of obstruction (mechanical)	Cause of obstruction (adynamic)
Esophagus	Atresia, Zenker's diverticulum, esophageal webs, goiter, foreign body impaction (food bolus), thoracic aortic aneurysm, benign and malignant strictures, Schatzki's ring, hiatal hernia	Scleroderma, achalasia, pharyngo-esophageal dysmotility (following stroke)
Gastric	Peptic ulcer disease, bezoars, gallstones, carcinoma, caustic injury, gastric volvulus	Diabetic gastroparesis
Small bowel	Annular pancreas, superior mesenteric artery syndrome, midgut volvulus, meconium ileus, adhesions, neoplasms, hernia, strictures, gallstone ileus	Mesenteric vascular occlusion, adynamic ileus (secondary to trauma, shock, peritonitis, metabolic/electrolyte imbalance, medications)
Large bowel	Carcinoma, volvulus (sigmoid, cecal), stricture (diverticular disease, ischemic colitis, radiation), intussusception	Constipation, pseudo-obstruction (trauma, shock, peritonitis, metabolic/electrolyte imbalance, sepsis, medications)

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in esophageal, gastric outlet and high SBO, central in low SBO, and generalized in LBO [49, 50]. Constipation may be absent initially in bowel obstruction due to continued peristaltic activity distal to the obstruction [50]. It may also be absent in partial bowel obstructions (adhesions, Richter's hernia), gall stone ileus, mesenteric vascular occlusion, and in ileus duplex. Continued vomiting, anorexia, and sequestration of fluid in the proximal bowel leads to dehydration, which manifests as fatigue, weakness, dizziness, and syncope.

Physical examination may reveal fever, tachycardia, hypotension, and mental status changes suggesting shock and sepsis (present in ischemic bowel or perforation). Abdominal distention, visible intestinal peristalsis, and hyperactive bowel sounds may be present. Abdominal scars indicating prior surgery is characteristic of adhesion-related obstruction. Guarding and rebound tenderness on palpation or percussion suggests ischemic bowel or peritonitis. Mass over a hernial orifice (inguinal, femoral, umbilical, incisional) is consistent with an irreducible and possibly obstructed hernia. A tense or tender hernia with a history of recent increase in size and absent cough impulse is characteristic of strangulated contents. The rectal examination shows an empty and ballooned rectum.

Investigations

Laboratory studies may show leukocytosis, hypochloremic, hypokalemic metabolic alkalosis (due to vomiting), elevated BUN, and serum creatinine (reflecting dehydration and poor renal perfusion). Elevated lactic acid and metabolic acidosis suggest gangrene, peritonitis, and sepsis [51]. Increased levels of intestinal fatty acid binding protein (I-FABP) has been detected in intestinal ischemia.

Plain abdominal x-rays (low sensitivity – 66%) may confirm both presence and level of bowel obstruction. In patients with high complete SBO, there is little air in the bowel, whereas more distal obstructions produce a "stepladder" pattern of air-fluid levels within bowel loops on erect abdominal x-rays. Presence of 2 or more air-fluid levels, differential air-fluid levels in the same loop of bowel and a mean air-fluid level width of at least 25 mm is very characteristic of high-grade SBO [52]. On supine abdominal x-rays, distended jejunal (identified by mucosal folds traversing the breadth of the lumen – valvulae conniventes) and ileal loops (featureless) are seen. With colonic obstruction, distended colon (identified by haustral folds, not traversing the width of the bowel) is seen. Using contrast (barium or diatrizoate meglumine – gastrografin) to outline the bowel helps delineate the site of obstruction and the transition zone. The contrast can be ingested orally or infused into the duodenum (enteroclysis); it can also be combined with CT (CT enteroclysis – specificity 100%; sensitivity 88% in SBO) [52]. Oral contrast is avoided in suspected bowel ischemia or perforation. Barium, diatrizoate, or air enemas are successful in reducing intussusception in the majority of children (70–84%) [7]. Diatrizoate, though safer than barium, does not provide mucosal detail, and its hygroscopic effect may exacerbate intravascular hypovolemia and electrolyte imbalance.

CT has high sensitivity (90–95%) and specificity (96%) in identifying high-grade bowel obstruction (distended proximal and collapsed distal bowel), locates transition zone and also diagnoses volvulus, ischemia (bowel thickening, poor IV contrast filling), perforation, and gangrene (pneumatosis intestinalis, pneumoperitoneum, mesenteric fat edema, ascites) [49]. CT also helps identify those patients without initial clear indications for emergent surgery, likely to fail conservative management and benefit from early intervention. Schwenter et al. devised a scoring system incorporating multiple variables (clinical, laboratory, and CT parameters) into a model (pain $\geq$4 days, guarding, C-reactive protein $\geq$75 mg/L, white cell count $\geq 10 \times 10^9$/L, ascitic fluid volume $\geq$ 500 mL on CT, reduced CT small bowel wall contrast enhancement), and found that the risk of intestinal ischemia was 6% in patients with score $\leq$ 1. Scores $\geq$3 are highly suggestive of ischemia (sensitivity 67.7%, specificity 90.8%) making surgery more likely to be considered in these patients [53]. Bedside US is an option in unstable patients and during

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pregnancy. US is extremely sensitive (98–100%) and specific (88–100%) in diagnosing intussusception. It is noninvasive, rapid, involves no radiation, identifies the apex of the intussusception, provides information regarding reducibility, and monitors reduction; it also identifies alternative diagnoses [7]. MRI also has both high sensitivity (95%) and specificity (100%) for SBO and LBO [54]. Colonoscopy is useful in confirming the diagnosis of LBO when in doubt, obtaining biopsies of obstructing lesions, derotating sigmoid volvulus, decompressing pseudo-obstruction, stenting strictures, and avoiding unnecessary surgery [55] .

Bowel Obstruction: Treatment

Principles of treatment include intravenous hydration, bowel rest, bowel decompression by nasogastric suction, correction of fluid and electrolyte imbalance, ascertaining the level and cause of obstruction, and determining need for emergent surgery. Prompt surgery is essential after resuscitation in patients with frank peritonitis, suspected ischemic/necrotic bowel, closed loop obstructions, in patients with obstructed/irreducible hernias, and in patients with volvulus or intussusception not responding to endoscopic derotation or hydrostatic reduction respectively. Surgery is also indicated if conservative measures do not result in clinical improvement (optimal duration of conservative management is controversial) and if progressive hemodynamic instability and acidosis point to worsening ischemia or sepsis. Fever, leukocytosis, acidosis and hemodynamic instability, or clinical evidence of peritonitis or bowel ischemia also indicates initiation of broad-spectrum antibiotic therapy (effective against gram-negative organisms and anaerobes).

Surgery may involve laparotomy or laparoscopy, release of adhesions, segmental resection of ischemic or obstructing segments of small/large bowel, and primary anastomosis in the absence of infection or peritoneal contamination. In the presence of active peritoneal sepsis or spillage of bowel contents, the healthy bowel ends are sutured to the skin (jejunostomy, ileostomy, colostomy); the ends re-anastomosed after patient recovery a few weeks later. Antibiotics are continued until infection resolves. Patient characteristics predicting increased postoperative morbidity (12–47%) include older age, comorbid illness (cerebrovascular accident with neurological deficit, CHF, chronic obstructive pulmonary disease), leukopenia ($<4500/mm^3$), renal dysfunction (creatinine >1.2 mg/dL), and poor functional status. Wound contamination or infection and resection of bowel also predict increased postoperative morbidity [56]. Advanced age, higher ASA class (≥ 3), chronic illness, treatment delay, and bowel ischemia predict higher mortality [49].

Complications of surgery include hemorrhage, wound infection, intra-abdominal collections, inadvertent trauma to bowel, nerves, vessels, ureter or solid organs (liver, spleen, kidney), recurrent obstruction, atelectasis, pneumonia, respiratory failure requiring ventilator support, urinary tract infection, and renal failure.

Surgical Problems of the Digestive System: Prevention

Lifestyle changes including seat belt use, defensive driving, minimizing alcohol use, and avoiding recreational drug use will decrease abdominal trauma associated with motor vehicle accidents. Incidental appendectomy, though an option and generally safe, is not recommended but may have some value in women presenting with undiagnosed abdominal/pelvic pain as part of laparoscopic evaluation [57] Incidental cholecystectomy is recommended in patients prone to develop cholelithiasis and cholecystitis (hemolytic disorders, gall bladder polyps, and cholesterolosis, Porcelain gallbladder and those with large gall stones- over 3 cm) [58] Maintaining ideal body weight, exercising, repairing symptomatic hernias, and meticulous operative technique and postoperative care will reduce risk of hernia-related complications and recurrence. No surgical technique has been found to reduce the risk of adhesions causing bowel obstruction significantly, though minimal manual trauma to the intra-abdominal structures,

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omental interposition between the abdominal wall and intra-abdominal organs, and excluding foreign materials in the peritoneal cavity (sutures) help.

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Selected Disorders of the Digestive System

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Jason Domagalski

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Acute Diarrheal Illness

General Principles

Acute diarrheal illness is a common presenting condition in primary care with the majority of cases attributed to viral gastroenteritis. Acute gastroenteritis in children under the age of five leads to 300 deaths, over 1.5 million outpatient visits, and 200,000 hospitalizations in the United States every year [1]. Annual deaths attributed to diarrheal illness are estimated to be 2.5 million worldwide [2].

Acute diarrhea is defined as increased stool frequency as well as increased water content and volume lasting less than 14 days [3]. Viral infections are the most common etiology of acute diarrhea, with rotavirus attributing to 75–90% of cases in children [1]. Bacterial pathogens are more likely with recent travel, foodborne illness, or immunocompromised states. The most common bacterial causes of acute diarrhea in the US include enterohemorrhagic *E. coli*, *Clostridioides (formerly clostridium) difficile*, *Shigella*, *Salmonella*, and *Campylobacter* [4].

Approach to Patient

The initial approach to a patient presenting with acute diarrheal illness should include a thorough history and physical exam evaluating the following questions:

1. What is the onset, duration, and consistency of the stool (i.e., bloody, watery, bilious)?
2. Is the patient showing signs of dehydration (i.e., thirst, decreased urine output, dizziness)?
3. Has there been any recent travel?
4. Is the patient vomiting (suggestive of a viral illness or foodborne illness)?
5. Is the patient showing signs of invasive bacterial diarrhea (i.e., fever, tenesmus, and grossly bloody stool)?
6. Is the patient pregnant (pregnant women are 12 times more likely to contract listeriosis)?
7. Is there any history of other gastroenterologic disease or surgery (i.e., partial colectomy or celiac disease)?
8. Any risk factors for immunosuppression? (i.e., human immunodeficiency virus, long-term steroid use, chemotherapy).

Diagnosis

Diagnostic testing is not typically indicated for acute diarrheal illnesses; however, further investigation is warranted for patients with longer duration of illness, signs of dehydration, history of being immunocompromised, or historical features indicating a serious bacterial infection. Common characteristic features and management of the covered pathogens are summarized in Table 1.

Lactoferrin is the preferred test for identifying leukocytes in the stool as a marker of inflammation. Fecal leukocytes lack the sensitivity and specificity

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Table 1 Clinical features and management of acute diarrheal illness

Pathogen	Historical features	Symptoms	Management
Viral (*Norovirus*, *Rotavirus*)	Variable, increased risk in day care centers, group living	+/− fever, abdominal pain, nausea/vomiting	Hydration, antipyretics, antispasmodics, loperamide/ Lomotil
Salmonella	Consumption of raw milk, undercooked meat, fecal-oral sexual contact	Fever, abdominal pain, +/− nausea, +/− bloody stool	Hydration, antipyretics, antispasmodics
Clostridioides difficile	Hospital admission, antibiotics within past 3 months	+/− fever, +/− abdominal pain, +/− bloody stools	Oral vancomycin 125 mg qid × 10 days, fidaxomicin 200 mg bid for 10 days
EHEC	Consumption of raw beef, seed sprouts, raw milk	No fever, abdominal pain, bloody stool	Oral/intravenous hydration

compared to lactoferrin which is >90% and >70%, respectively [5]. Positive occult blood in combination with lactoferrin increases the likelihood of an inflammatory diarrhea. Stool cultures are rather expensive and should only be reserved to use in patients with grossly bloody diarrhea, severe dehydration, history of immunosuppression, or signs of inflammatory disease [6]. Testing for *Clostridioides difficile* toxins A and B is indicated in any patient that develops diarrhea after 3 days of hospitalization, during any antibiotic course or up to 3 months after an antibiotic course is discontinued. Testing for ova and parasites is indicated in patients with diarrheal illnesses exceeding 7 days along with one or more features: patients with AIDs, men who have sex with men (MSM), bloody diarrhea with few fecal leukocytes, community waterborne outbreaks, children attending daycare, or recent travel to mountainous regions [7]. Endoscopic evaluation is often of limited use and should be reserved for those patients with unclear diagnosis after routine blood and stool tests are negative, if empiric therapy is ineffective or if symptoms persist [8].

Treatment

Viral Infections

Viral gastroenteritis accounts for the majority of diarrheal illnesses with the most common causative viruses being *Rotavirus*, adenoviruses, echoviruses, and reoviruses. Ambulatory management generally involves avoidance of solid foods for the first 24–48 h and fluid replacement with oral rehydration with commercially available products (Pedialyte) or following the 2002 World Health Organization-endorsed reduced osmolarity oral rehydration solution by combining 1 l of water, six teaspoons of sugar, and half teaspoon of salt [*8*]. Antidiarrheal agents such as loperamide (Imodium) or diphenoxylate/atropine (Lomotil) may also be used to reduce duration of illness in patients with nonbloody stool.

Bacterial Infections

Salmonella

Typically associated with *typhimurium* serotype, *Salmonella* induces mild enteritis associated with fever, nausea, and vomiting which is self-limited to less than 4 days duration. Management is usually supportive in nature with oral rehydration and antispasmodics. Antibiotics are not generally indicated as they will prolong the carrier status [8].

Enterohemorrhagic *Escherichia coli* (EHEC)

Typically associated with the consumption of raw seed sprouts, unpasteurized juice, and undercooked poultry or hamburger meat, EHEC may produce severe symptoms to include bloody diarrhea and multisystem organ failure in the very young or old. Also commonly known as Shiga toxin producing *E. coli* (STEC), EHEC typically is managed with supportive care and IV hydration when necessary. Antibiotics are often cautioned against as their use may increase risk of developing hemolytic uremic syndrome (HUS) in which

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the patient develops thrombocytopenia, hemolytic anemia, and renal failure [8].

Clostridioides Difficile

Clostridioides (formerly clostridium) difficile infections are commonly associated with nosocomial-induced diarrhea as well as diarrhea that develops during or soon after antibiotic exposure. *C. difficile* infection is 7–10 times more likely during any point of an antibiotic course [8]. Major complications include fulminant colitis, toxic megacolon, intestinal perforation, and even septic shock. First-line management for nonsevere disease is oral vancomycin 125 mg qid for 10 days or oral fidaxomicin 200 mg bid for 10 days. Metronidazole 500 mg qid for 10 days is an acceptable alternative if the other two agents are unavailable, but should be avoided in patients who are elderly, infirmed, or who have developed the infection in association with inflammatory bowel disease. Oral vancomycin or oral fidaxomicin are more appropriate for severe infections. Although both are effective, recurrence with *Clostridium difficile* is as high as 15–25%. For recurrent or severe infections, fecal transplant from a healthy donor is a viable treatment strategy [9].

Prevention/Family and Community Issues

General hygiene and hand washing can prevent the majority of diarrheal illnesses. Certain populations should avoid high-risk behaviors. Patients with heavy alcohol use or people with chronic liver disease consuming shellfish as they are at risk for contracting *Vibrio vulnificus*. Pregnant women are at risk for being infected with *Listeria monocytogenes* from soft cheeses and unheated deli meats. Vaccines currently available include those to prevent *Rotavirus* in small infants and typhoid fever for travelers [3].

Ischemic Bowel Syndromes

General Principles

The colon can tolerate significantly reduced blood flow with up to 80% of capillaries not perfusing during bowel rest without sacrificing adequate oxygen delivery [10]. Compromise of blood flow to the colon can present as an acute or chronic process and is always secondary to an underlying disease process ranging from trauma to a hypercoaguable state. Acute mesenteric ischemia is a rare but fatal condition with an incidence of only 12.9 per 100,000 person-years and a mortality rate greater than 50% [10, 11]. The four major conditions that cause acute mesenteric ischemia include acute superior mesenteric artery (SMA) thromboembolic occlusion, mesenteric arterial thrombosis, mesenteric venous thrombosis, and nonocclusive mesenteric ischemia.

Approach to Patient

The common clinical triad of acute bowel ischemia includes severe abdominal pain out of proportion to physical exam, bowel emptying, and a source of occlusion or decreased blood flow [10]. Chronic ischemia will typically present with a history of postprandial pain (intestinal angina), fear of food, and weight loss. Prompt diagnosis requires a high index of clinical suspicion, focused history and physical exam, and prompt ordering of a high-resolution CT [11]. Common conditions associated with mesenteric ischemia include atrial fibrillation, congestive heart failure, hypovolemia, hypercoaguable states, portal hypertension, and major trauma [11].

Diagnosis

There is no one single plasma marker sensitive enough to make an early diagnosis [10]. Signs of metabolic acidosis on arterial blood gas and metabolic panels are often a late finding indicating bowel infarction. Other lab markers of early bowel ischemia include elevated levels of amylase and lipase [11]. An elevated white blood cell count or left shift may indicate a full-thickness injury or ischemia with bacterial translocation [12].

Diagnosis typically requires early ordering of abdominal CT with contrast. This allows complete evaluation of both the mesenteric arterial and venous patency. The use of mesenteric vessel angiography has diminished due to the efficiency and

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availability of CT scans for acute ischemia but still may have high utility in the workup of chronic mesenteric ischemia [11]. Magnetic Resonance Angiography is another option, but is limited due to duration of test, lacks necessary resolution, and can overestimate degree of stenosis [12].

Treatment

Acute Mesenteric Ischemia

The approach to management of acute bowel ischemia relies on three essential principles: the cause of the ischemia, severity of presentation, and duration of compromised blood flow. Another key aspect in management is the availability of therapeutic procedures in interventional radiology as well as vascular surgery.

Acute SMA Occlusion

Initial treatment in stable patients includes aggressive parenteral fluid replacement, bowel decompression with nasogastric tube, and/or broad-spectrum antibiotics if sepsis is suspected. In patients with suspected bowel infarction, immediate exploratory laparotomy is warranted. Embolic obstructions require surgical embolectomy of the superior mesenteric artery as the occlusions are typically secondary to a cardiac thrombus and not amenable to thrombolysis due to the high risk of fragmentation and distal embolization [11]. Mesenteric arterial thrombosis due to chronic atherosclerotic occlusive disease of the SMA however is more amenable to endovascular techniques with stenting when possible. Despite this less-invasive approach, exploratory laparotomy may still be necessary to assess the recovery of the ischemic bowel. In more severe cases, aorto-mesenteric bypass may be necessary [11].

Acute Mesenteric Venous Thrombosis

Mesenteric venous thrombosis is best treated medically with anticoagulation using continuous infusion of unfractionated heparin and restoration of circulating blood volume with parenteral fluid replacement. Nonsurgical management has been documented to have as high as 80% 30-day survival rate [10]. Surgical management is reserved for patients with signs of bowel infarction requiring resection of necrotic bowel [11]. Necrosis typically occurs when venous engorgement obstructs arterial blood flow. When surgery is performed, it often requires extensive removal of affected bowel, and prognosis is typically poor. Patients who do recover often undergo extensive bowel removal and subsequently suffer from short gut syndrome [11].

Nonocclusive Disease

Almost always secondary to critical illness, nonocclusive ischemia is often associated with cardiopulmonary insufficiency and treatment of septic shock. Management is limited to replenishing mesenteric circulation and observing for early signs of infarction. Ischemic colitis, a type of nonocclusive ischemia, typically responds to medical management with bowel rest, broad-spectrum antibiotics, and fluid replacement in up to 60% of cases. Exploratory laparotomy is warranted with any type of nonocclusive ischemia if patients begin to develop signs of peritonitis or clinical decompensation indicating possible bowel infarction [11].

Chronic Mesenteric Ischemia

Chronic mesenteric ischemia is an uncommon condition and more than 90% of cases are related to progressive atherosclerotic stenosis of one or more mesenteric arteries [13]. The goals of management are to resolve patient symptoms, improve nutritional status, and prevent possible infarction. When attempted, revascularization with angioplasty and possible stent placement should be as complete as possible. Stent placement is typically warranted when post-angioplasty residual stenosis is 30% or greater, the area of involvement has a high-pressure gradient or the patient has a history

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of dissection with prior angioplasty attempts. Open surgical revascularization can be considered if endovascular approach failed, contraindications to radiation or contrast exist or if endovascular technique is not technically possible due to extensive occlusion [13].

Prevention and Family and Community Issues

Patients at risk for developing atherosclerotic disease should be managed for maximal risk reduction with smoking cessation as well as management of hypertension and hyperlipidemia. Patients with hypercoaguable states or strong family history of hypercoagulability should be advised on risks of medications that may increase the risk of thrombosis. Any patients with the above risk factors should be made aware of the signs and symptoms of bowel ischemia and advised to seek immediate medical attention if symptoms develop.

Food Allergy

General Principles

The exact prevalence of food allergy is unknown; however, recent studies indicate that it affects anywhere from 2% to 10% of the population with approximately 8% of children in the United States having one food allergy, 2.4% having multiple, and approximately 3% having a history of severe reactions. The most common offenders are cow's milk, peanuts, and tree nuts in children while shellfish, fruits, and vegetables being the most common in adults. Although somewhat unclear, epidemiologic studies are indicating a potential rise in food allergies among children in the United States over the last 2–3 decades [14].

Multiple risk factors are associated with food allergy development as listed in Table 2 and may provide areas of intervention to prevent food allergies. Resolution of childhood allergies to milk, eggs, wheat, and soy is common whereas allergies to peanut, tree nuts, fish, and shellfish tend to persist.

Table 2 Risk factors for food allergy

Modifiable risk factors	Nonmodifiable risk factors
Reduced consumption of dietary fat	Male gender (in children)
Reduced consumption of antioxidants	Black ethnicity
Obesity	Asian ethnicity
Vitamin D deficiency	Atopic dermatitis
Increased hygiene	

Approach to Patient

Common assessment for potential food allergies should include the following historical clinical questions:

1. What symptoms does the patient develop (urticaria versus more severe symptoms such as airway compromise)?
2. Does the patient suffer from other signs of atopic disease (eczema or asthma)?
3. Does the patient have any history of difficulty swallowing or choking with known food exposure (indicating possible underlying eosinophilic esophagitis)?
4. Does the patient suffer from an underlying metabolic disorder (lactose intolerance versus true milk allergy)?

Diagnosis

Identifying an underlying food allergy requires careful review of clinical history and familiarization with common clinical manifestations. It is also necessary to be aware of common conditions that appear similar to but are not true food allergies. Examples include gustatory rhinitis in which spicy foods induce rhinorrhea, scombroid fish poisoning where spoiled dark meat fish release histamine-like toxins, and aurico-temporal syndrome where foods that trigger salivation may also induce vasodilation in the capillaries of the lower cheek [14].

General approaches to diagnosis include elimination diets, skin prick testing, serologic IgE measurements, and oral food challenges [15]. Although commonly avoided, oral food challenges can be

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very beneficial as many food triggers may not be true allergies allowing for significant expansion of the affected patient's diet. There is also a low risk of severe reaction, but up to 3% can have reactions to the food later despite tolerating it during testing [14].

Treatment

The first-line approach to management is avoidance of the offending agent(s) and preparation to respond to allergic responses. This requires education on prehospital treatment, appropriate use of subcutaneous epinephrine, label reading, and when to seek medical attention.

Prevention/Family and Community Issues

Previous recommendations of allergen avoidance both in pregnancy and early childhood have for the most part been rescinded in general guidelines for food allergy prevention [15]. Newer studies have shown regular exposure to common allergens such as peanuts during pregnancy may actually reduce the likelihood of atopic disease [16]. Studies have also shown that delayed introduction of common food allergens is also not protective and may even increase risk of developing food allergies [14]. In one large study, introduction of peanuts to high-risk infants (severe eczema and or known egg allergy) had only a 10% rate of peanut allergy when peanuts were introduced at 4–6 months compared to 35% when peanut introduction was avoided until 5 years of age [14].

Lactose Intolerance

General Principles

Lactose is digested primarily in the small intestine where it is broken down by the enzyme lactase into glucose and galactose. In lactase-deficient individuals, lactose is passed to the colon where gut flora break it down to small-chain fatty acids and gas by-products of hydrogen, methane, and carbon dioxide. The main cause of lactose intolerance is downregulation of lactase resulting in lactose malabsorption. Lactose intolerance is defined as a constellation of symptoms to include abdominal pain, bloating, and/or diarrhea secondary to lactose malabsorption. The worldwide prevalence of lactose malabsorption is 68% with the lowest occurrence in Nordic countries (<5% in Denmark) and highest in Korea and Han Chinese populations (close to 100%) [17]. It is also important to point out that lactase deficiency may be secondary to another condition such as those listed in Table 3.

Table 3 Conditions that may contribute to lactose malabsorption

Acquired	Disease related
Gastrointestinal surgery	Systemic sclerosis
Small bowel bacterial overgrowth (SBBO)	Celiac disease
Infectious enteritis (giardiasis)	Inflammatory bowel disease
Medications	Short bowel syndrome
Radiation enteritis	

Approach to Patient

Common complaints of a patient with lactose intolerance may include diarrhea, flatulence, bloating, abdominal pain, and borborygmi. Systemic findings may include failure to thrive in children, skin disease, chronic fatigue, and rheumatologic complaints in adults [17].

Diagnosis

Lactose intolerance was recently defined by the NIH as "the onset of gastrointestinal symptoms following a blinded, single dose challenge of ingested lactose by an individual with lactose malabsorption along with absence of symptoms when the person ingests an indistinguishable placebo" [18]. Despite this recognized definition, this test is not currently performed in clinical practice. Objective testing for lactose intolerance includes duodenal biopsies, genetic testing, lactose

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tolerance test, serum gaxilose test, urine galactose test, and H2 breath test.

Although being the reference standard and offering the advantage of ruling out other conditions that may affect the small intestine such as celiac disease, mucosal biopsies of the duodenum hold the highest expense, and are the most invasive of all other testing. Genetic testing for the −13,910: C/T genotype, which evaluates for lactase nonpersistence in Caucasian patients, had a high correlation with other tests for lactose malabsorption within European countries. The test, however, is of limited use in other ethnic groups and would have false-negative results in individuals with secondary causes for clinical lactose intolerance. The lactose tolerance test and H2 breath test are both performed after an oral challenge with a standard dose of lactose. The lactose tolerance test measures change in serum glucose while the breath test measures the hydrogen gas produced by intestinal bacteria in expired air. The serum gaxilose and urine galactose test are detection of D-xylose in the serum or galactose in the urine after given gaxilose orally [17].

Treatment

General reduction of lactose intake instead of complete exclusion should be advocated as the majority of patients can tolerate a minimum of 12 g of lactose, which is equivalent to 8 oz. of milk, without symptoms. Patients with symptoms in smaller amounts should bring into question the possibility of a cow's milk protein allergy. Lactase enzyme replacement is another option, but it does cause a change in flavor due to the breakdown of lactose to the much sweeter sugars glucose and galactose. Probiotics may also offer improvement in patients with concomitant IBS by altering gut flora. Studies have also shown potential for prebiotics by way of manipulating microbiota with one study showing over 20% improvement in lactose tolerance after only 1 month worth of treatment [17]. Tolerance may also be improved by successive increases in lactose ingestion [19].

Prevention/Family and Community Issues

Dietary education for populations at risk and adapting modified menus for broad population dietary programs such as school lunches or adult care facilities are the main modes of prevention.

Marine Poisoning

General Principles

Although more common in coastal rural communities of the Pacific with an annual incidence of 1200 per 100,000, marine poisoning is being seen in rising numbers after consumption of imported seafood or by travelers to these areas [*20*]. The three major clinical syndromes that may present with neurologic sequelae include ciguatera, shellfish poisoning, and tetrodotoxin poisoning.

Approach to Patient

Key factors to identify and evaluate for in the workup of a patient with possible marine poisoning include:

1. Type of seafood consumed and timing of ingestion (reef fish associated with ciguatera and puffer fish with tetrodotoxin).
2. Severity of gastrointestinal symptoms (severe in ciguatera while mild with tetrodotoxin poisoning).
3. What are the neurologic symptoms (paresthesia more common with ciguatera while paralysis common with tetrodotoxin and shellfish poisoning)?

Diagnosis

Diagnostic tests are not clinically available in primary care settings; hence, diagnosis is based on clinical symptoms and consumption of offending marine agent within the preceding 24 h. Clinical characteristics of the most common marine poisoning syndromes are outlined in Table 4.

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Table 4 Common marine poisoning syndrome characteristics

Syndrome	Toxin	Source	Symptoms	Onset (hours)	Geographic origin
Puffer fish poisoning	Tetrodotoxin	Puffer fish, toadfish	Mild GI effects, descending paralysis, rapid progression to respiratory failure when severe	0.5–3	Southeast Asia, China, and Japan
Ciguatera	Ciguatoxins	Reef fish	Severe GI effects, myalgia, paresthesia, ataxia, rarely fatal	1–48	All tropical areas
Paralytic shellfish poisoning	Saxitoxin and gonyautoxin	Bivalve shellfish (mussels, oysters, clams)	Descending paralysis, respiratory failure when severe	0.5–4	NW/NE US, southern Chile, North Sea, Japan
Neurotoxic shellfish poisoning	Brevetoxin	Shellfish	Severe GI effects, paresthesia, "temperature reversal," vertigo	3–6	West Florida, Caribbean
Amnesic shellfish poisoning	Domoic acid (diatom algae)	Shellfish	Moderate GI effects, amnesia, CN palsies, seizures	GI <24; neuro <48	East Canada, NE and West USA

Treatment

As there are no clinically available antidotes, management is restricted to supportive care and mechanical ventilation when indicated [20]. Although an accepted treatment for ciguatera poisoning includes the use of IV mannitol, recent double-blinded studies have shown no significant clinical outcomes when compared to infusion of normal saline [21].

Prevention/Family and Community Issues

To prevent potentially fatal poisoning, travelers should use caution when consuming exotic seafood and consult medical travel resources and season-specific information. Shellfish harvesting is quarantined in areas of the United States and Canada at times when toxic sources such as dinoflagellates are the highest in concentration.

Botulism

General Principles

First described in the eighteenth century, botulism is a neurologic disorder induced by an anaerobic, gram-positive, spore-forming bacterium, *Clostridium botulinum*. Contraction of the infection typically follows consumption of honey in the case of infant botulism or affected foodstuffs such as home-canned foods and fermented uncooked dishes in foodborne botulism [22].

Approach to Patient/Diagnosis

The onset of symptoms after consumption of contaminated food often occurs within 12–36 h of ingestion. Presentation can vary with an onset of gastrointestinal symptoms (nausea, vomiting, diarrhea) followed by neurologic symptoms. Neurologic complaints of blurred vision and diplopia occur first followed by findings of slurred speech, dysphonia, and difficulty swallowing. Descending paralysis is a late finding leading to compromised diaphragm and intercostal muscles inducing respiratory failure [22].

Diagnosis is based on clinical suspicion, history of ingested food source, and physical exam findings. Definitive diagnosis can be made with toxin detection in serum, stool, or gastric aspirate; however, this should not delay treatment as clinical assays for detection may take days.

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Treatment

Management of suspected clinical botulism involves supportive care to include the use of mechanical ventilation as well as administration of the heptavalent antitoxin. The antitoxin is targeted against free toxin molecules to prevent paralysis and has little clinical effect on already paralyzed musculature [23].

Prevention/Family and Community Issues

Widespread education for parents of infants to avoid honey consumption for the first year of life as well as education on the risks of improperly home-canned and cured items is essential. Commercial canneries take special precautions to prevent clinical botulism by heating prepared foods to high temperatures or adding acidifying agents to prevent spore formation. Spores have shown to be destroyed by heating to 121 °C for a minimum of 2.5 min [22].

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Part XX

The Renal, Urinary, and Male Genital Systems

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Urinary Tract Infections

99

Mindy J. Lacey

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Urinary tract infections (UTIs) are defined as the presence of a significant number of pathogenic bacteria in appropriately collected urine and result in over seven million office visits with an estimated one million episodes annually of UTI-related illness requiring hospitalizations. Among children, 1 in 20 girls and 1 in 50 boys have a UTI each year [1]. The primary goal of UTI diagnosis and management is the prevention of long-term complications of progressive events that affect later-life morbidity or mortality. Major risk groups include school-age girls, young women in their sexually active years, pregnant women, males with prostate obstruction, and the elderly [2].

This chapter discusses important clinical issues in the following categories: UTI in children, UTI in pregnancy, acute uncomplicated lower UTI in young women, recurrent infection in women, acute uncomplicated pyelonephritis in young women, complicated UTIs, UTIs in younger men, catheter-associated UTIs, chronic UTIs in the elderly, UTIs with spinal cord injuries, and fungal UTIs.

Asymptomatic Bacteriuria

Except for pregnancy and prior to urologic surgery, screening for asymptomatic bacteriuria has no apparent value, and if incidentally found treatment is not necessary. Even among the elderly where there may be an association between asymptomatic bacteriuria and mortality, a causal link has not been demonstrated [3].

UTI in Children

For boys and girls, the incidence of symptomatic infection during the first 6 months of life is similar, but after 6 months to a year it falls off rapidly for boys. Among girls, the first-year incidence is more evenly distributed through the year. During the first 3 months of life, boys are more likely to be infected presumably related to not being circumcised. In neonates, the prevalence is threefold higher among premature infants [4]. In girls, the incidence steadily rises with a small transient increase at preschool period and remains level until sexual activity becomes a factor. Asymptomatic bacteriuria is not observed in boys until later in adult life when obstructive problems occur. In girls, asymptomatic bacteriuria is present early in infancy and remains fairly constant throughout the late teens [5].

The primary host-related factors that lead to the development of UTI include infancy, female sex, abnormal defense mechanisms, the presence of urinary tract abnormalities, sexual activity, lack of circumcision, and prior instrumentation [4]. In children without urinary tract abnormalities, periurethral bacterial colonization is a risk factor for UTI [6].

Escherichia coli accounts for as many as 80% of UTI [7, 8]. In neonates, *Proteus mirabilis* (mainly in boys), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter* species, *Staphylococcus aureus* (mainly in older children), *Streptococcus viridans*, enterococci, and *Candida albicans* should be considered [7].

Diagnosis

Urinalysis and Culture

In any febrile infant or child, the differential diagnosis should include UTI. Screening by urinalysis is first line in diagnosis; however, due to its relatively low sensitivity (approximately 90%), a negative urinalysis should be confirmed with culture. In a properly collected specimen (urethral catheterization or suprapubic aspiration in infants), a presumptive diagnosis can be made with the presence of any bacteria and five leukocytes per high-power field (hpf) [9].

Imaging Evaluation

Imaging should be conducted after the first episode of UTI in girls younger than 5 years, boys of any age, older sexually inactive girls with recurrent UTI, and any child with pyelonephritis [9]. Debate continues about the best radiologic approach for evaluation [10]. The issue centers around the role of radionuclide scans and how these methods may replace or be used in

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conjunction with traditional ultrasonography (US), voiding cystourethrography (VCUG), intravenous pyelography (IVP), and spiral computer-assisted tomography (CT).

Scintigraphic studies using 99 m-technetium dimercaptosuccinic acid (DMSA) has become a leading choice for gauging renal function, identifying renal cortical defects, and is the gold standard for diagnosis of acute pyelonephritis. However, it should not be used in routine evaluation of the child with a first UTI due to exposure to radiation [10–12]. When applied at 6–12 months after cortical defects have first developed, the DMSA scan may be the best test for renal scarring. US has the obvious advantage of being a noninvasive test that may rule out obstruction. Spiral CT is the first choice for the presence of obstructive stone disease. VCUG gives comprehensive lower tract information and allows grading the severity of reflux [10].

An imaging strategy can be summarized this way: use renal/bladder US to look for obstruction; use a DMSA scan to identify cortical defects and assess differential kidney function; use a VCUG to detect bladder anomalies, neurogenic defects, residual urine, and urethral abnormalities such as posterior valves, urethral strictures, and the presence of vesicoureteral reflux; and use spiral CT to determine the presence of stones [10].

Management

Early diagnosis and prompt treatment of UTI in infants and young children are crucial. With vesicoureteral reflux or other urinary tract abnormalities, immediate treatment reduces the risk of renal scarring. In the history, inquire about the defecation pattern. Physical examination should include a rectal examination to detect a large fecal reservoir, as fecal impaction can obstruct urine flow [13].

Symptomatic neonates should be treated for 7–10 days with a parenteral combination of ampicillin and gentamicin. Young infants with UTI, children with clinical evidence of acute pyelonephritis, and children with upper tract infection associated with urologic abnormalities or surgical procedures can be treated with a combination of an aminoglycoside and ampicillin, or an aminoglycoside and a third- or fourth-generation cephalosporin [4]. For complicated and uncomplicated infection, 7–14 days and 3–5 days of therapy recommended, respectively [10].

For uncomplicated UTI, first-line oral agents are cephalosporins. Alternatives include amoxicillin, trimethoprim-sulfamethoxazole or nitrofurantoin. Antibiotic treatment of asymptomatic bacteriuria in children is controversial. There is limited evidence that renal damage is prevented, or loss of function reduced, replacement of a low-virulence organism with a more virulent one may occur, and the child may experience long-term side effects from antibiotics [4]. A reasonable approach with asymptomatic bacteriuria is to treat children younger than 5 years or those who have urinary tract structural abnormalities.

UTI in Pregnancy

Pregnant women with UTIs are at greater risk for preterm birth and delivering infants with low birth weight or that are small for gestational age. There is strong evidence that UTI causes low birth weight through premature delivery rather than growth retardation [14]. In addition, there is increased risk of premature labor, hypertension/preeclampsia, anemia, and chorioamnionitis.

The risk of pyelonephritis from antepartum asymptomatic bacteriuria may be as high as 30%. Identification and eradication reduce this risk to less than 5%. Antepartum bacteriuria has an estimated prevalence of 2–7% [15, 16].

An optimal time for screening all pregnancies is at the first prenatal visit and urinalysis with culture should be obtained. If negative, no further studies are necessary unless there is a history of prior UTI or the patient becomes symptomatic. If the screening culture result is 10^5 colony-forming units (CFU)/mL or higher, treatment for asymptomatic bacteriuria should be undertaken.

Similar to nonpregnant females, *E. coli* is the most common cause of UTI and asymptomatic bacteriuria during pregnancy. Other organisms include *Enterobacter* species, *Klebsiella* species, *Proteus* species, and *Group B Streptococcus* [17].

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The first concern regarding treatment during pregnancy is the safety of antibiotics. Considered reasonably safe are penicillins, cephalosporins, and nitrofurantoin.

For asymptomatic bacteriuria, a regimen of 7–10 days is used; there is little support for single-dose therapy. Pyelonephritis is managed the same as in nonpregnant females.

Acute Uncomplicated Lower UTI in Young Women

Acute uncomplicated UTIs (cystitis and urethritis) are confined to the bladder and have no signs of systemic infection [3]. The risk is increased by sexual intercourse, delayed postcoital voiding, use of a diaphragm or spermicidal gel, and history of recurrent infections [18].

Cystitis pathogens include *E. coli*, *S. saprophyticus*, *Proteus* species, or *Klebsiella* species. Symptoms are abrupt in onset and include dysuria, increased frequency, and urgency. Suprapubic pain and low back pain may also occur, and pyuria and hematuria can be present.

Urethritis pathogens include *Chlamydia trachomatis*, *N. gonorrhoeae*, and herpes simplex virus. Symptoms are more likely to be gradual in onset and mild (including dysuria and possibly vaginal discharge and bleeding from a concomitant cervicitis) and include lower abdominal pain. Suspicion is raised if the patient has a new sexual partner or evidence of cervicitis on examination. Pyuria is also usually present.

With no multidrug resistance (MDR) in the community, reasonable empiric treatment prior to organism identification includes nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX), or fosfomycin.

Acute Uncomplicated Pyelonephritis in Young Women

Findings suggestive of uncomplicated upper tract parenchymal involvement can include fever and flank pain. Urine culture and sensitivity should be performed in all patients with known or possible acute pyelonephritis. This process allows for alteration of empiric treatment.

Characteristic pathogens in acute uncomplicated pyelonephritis in young women include *E. coli*, *Proteus mirabilis*, *K. pneumoniae*, and *S. saprophyticus*. Outpatient management is reasonable for mild to moderate illness without nausea and vomiting. A 10–14-day regimen of the following is appropriate: oral TMP-SMX, ciprofloxacin, and levofloxacin are first line until an organism and sensitivities are available. For severe illness requiring hospitalization, the following regimen can be followed: parenteral fluoroquinolone, aminoglycoside with or without ampicillin, extended-spectrum cephalosporin, an extended-spectrum penicillin, or a carbapenem [19].

Complicated UTIs

Complicated UTIs may present in the same way as uncomplicated but extends beyond the bladder. They occur in urinary tracts that have a functional, metabolic, or anatomic derangement predisposing to an infection that is more resistant to typical therapeutic measures. This infection should be suspected in patients with systemic symptoms such as fever, chills, malaise, flank pain, costovertebral tenderness, as well as pelvic/perineal pain in men.

Characteristic organisms include *E. coli*, *Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, enterococci, and staphylococci.

Antibiotic selection includes levofloxacin or ciprofloxacin if MDR is low. For severe illness requiring hospitalization, intravenous ceftriaxone is an appropriate first line choice. If MDR is high, then pipercillin/tazobactam should be used. This regimen should be continued until that patient is afebrile and then may be changed to oral therapy with either TMP-SMX, amoxicillin-clavulanic acid, or cefdinir for a total of 14–21 days [3]. Results of urine culture sensitivities and susceptibilities should be followed to be certain the antibiotic is appropriate.

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Recurrent Infections (Cystitis) in Women

Recurrent cystitis is defined as recurrence of symptoms within 2 weeks of completing therapy with the same pathogen, or if more than two infections in 6 months or three annually.

For fewer than two incidents of UTI per year, therapy can be started based on symptoms using either single-dose or 3-day therapy. For three or more UTIs per year, the relation to coitus must be considered. If the UTI is not related to coitus, a low-dose antibiotic daily or three times weekly is recommended, and treatment is commonly continued for 3–6 months [20]. If related to coitus, a single low-dose postcoital treatment may be preferable.

UTIs in Younger Men

Without underlying structural urologic abnormalities, risk factors for UTIs in young men include lack of circumcision, intercourse with other men and a sexual partner colonized with uropathogens [3, 21]. Symptoms include dysuria, urinary frequency/urgency +/− suprapubic pain or perineal pain. Pyuria and bacteriuria are typically present.

Management of symptomatic cystitis without obvious complicating factors requires urinalysis and urine culture to establish the pathogen. This step establishes sensitivity and helps in the event of recurrence. Once the culture is obtained, antibiotic choices include nitrofurantoin, TMP-SMX, or fosfomycin.

The traditional approach of undertaking a thorough post-UTI evaluation to rule out a urologic abnormality has been disputed [22, 23]. If pursued in young men who have responded to treatment, the probability of finding a urinary tract defect is low [24].

Catheter-Associated UTIs

Catheter-associated UTI (CAUTI) is the most common acquired infection in long-term-care facilities, and in the intensive care setting, with 95% of nosocomial UTIs being catheter-associated [25]. The presence of an indwelling catheter for at least 3 days has been identified as a risk factor with a 3–10% incidence of UTI per day of catheterization. CAUTI is a significant cause of morbidity and mortality in this population [26, 27].

Causative organisms are like those of complicated UTIs. *E. coli* and *Enterbacteriaceae* are the most common. Other pathogens include *Pseudomonas aeruginosa*, *K. pneumoniae,* enterococci, and candida species [28, 29]. Yeast may become an isolated pathogen when antibiotics are in use [25, 28].

Treatment in this setting depends on the clinical presentation: baseline prevention, antimicrobials for asymptomatic bacteriuria, symptomatic lower UTI and symptomatic (complicated) upper UTI. Treatment is typically 7–14 days. Prevention focuses on avoiding catheterization if possible. If catheterization is mandatory, the duration should be minimized, and a closed drainage system used.

Chronic UTIs in the Elderly

UTI is the most common infectious illness in adults aged 65 and older [39, 40]. Age-related physiologic changes play a role in UTI development including lack of estrogen in women, diminished prostatic secretion in men [30], and altered bacterial adhesion factors in both sexes.

Whereas *E. coli* and *S. saprophyticus* are the most common cause of UTI in young adults, some significant shifts in causative organism occur with the elderly. *E. coli* remains the most common causative organism with *Enterococcus faecalis* and *Klebsiella* species following [31].

The presentation of UTIs among the elderly can be similar to that of younger patients. However, these signs and symptoms can be absent with patients presenting as fever of unknown origin, altered mental status (lethargy), gastrointestinal complaints, incontinence, or respiratory symptoms [32]. Pharmacologic therapy and duration of treatment are similar to that in other age groups [33].

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UTI in Patients with Spinal Cord Injuries

UTI is the most frequent infection in patients with spinal cord injuries and occurs at a rate of 2.5 episodes/patient/year [34]. Special considerations for increased risk of UTI with spinal cord injuries include bladder overdistention, vesicoureteral reflux, high-pressure voiding, large postvoid residuals, stones in the urinary tract, and outlet obstruction [35]. Management focuses primarily on proper drainage of the bladder with intermittent catheterization reducing the risk of significant bacteriuria. Development of bacteriuria is common with indwelling and suprapubic catheters [36]. Asymptomatic UTIs are generally not treated and in general there is no role for prophylactic antibiotics as they may result in emergence of resistant bacteria [37].

Fungal UTIs

Fungal UTIs are common in hospitalized patients and are typically asymptomatic [38, 39]. Risk factors include urinary tract drainage devices, prior antibiotic therapy, diabetes, urinary tract pathology, and malignancy [40]. Common pathogens include *Candida albicans, Cryptococcus neoformans,* or *Aspergillus* species.

For asymptomatic colonization with *Candida,* no specific antifungal therapy is required unless there is a high risk of dissemination (neutropenia and very low birthweight (<1500 g)) or urinary tract manipulation [41]. Symptomatic patients should be treated, and fluconazole is the preferred agent if there is no resistance.

Treatment of asymptomatic infections is no longer mandatory in renal transplant patients. Therapy is considered on a case by case basis and undertaken only if there is a high risk of graft involvement or if the patient has ureteral stents [42].

Laboratory Guides and Interpretation

Pyuria

From a practical standpoint, pyuria represents measurable evidence of host injury. The most accurate method of defining significant pyuria is the leukocyte excretion rate and there is evidence that 400,000 white blood cells (WBC)/h is significant [43]. This measurement is cumbersome – hence the popularity of quicker, simpler, but less accurate screening tests. Those screening tests include microscopic examination of unspun urine in a counting chamber (WBC/mm^3), spun urine under a coverslip (WBC/hpf), and leukocyte esterase [44]. Diagnostic information related to these tests is displayed in Table 1.

Bacteriuria

Urine culture is considered the gold standard for defining significant bacteriuria. All other tests are simply screening devices chosen to balance immediacy of results and ease of performance with accuracy. The most common tests are direct microscopy and the urine dipstick (nitrite and leukocyte esterase). Commonly used screening tests with approximated diagnostic information are shown in Table 1.

Urine Culture

Urine cultures are not 100% sensitive or specific. The colony count that represents significant bacteriuria varies with age, sex, anatomic location of the infection, and symptoms. Colony counts of what can currently be considered as significant bacteriuria for infection are shown in Table 2.

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Table 1 Diagnostic value of the positivity of commonly used urine screening tests, individually and in various combinations

Screening test	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Nitrite (present or absent)	0.5	0.95	10.00	0.53
Bacteria				
Unstained, spun (2+ on scale of 4+)	0.75	0.8	3.75	0.31
Gram stain, unspun (1/hpf)	0.8	0.85	5.33	0.24
Microscopic pyuria				
Spun (5 WBCs/hpf)	0.6	0.85	4.00	0.47
Unspun (50 WBC/mm^3)	0.65	0.9	6.50	0.39
WBCs + bacteria				
Standard spun[a]	0.66	0.99	66.00	0.34
Enhanced unspun[b]	0.85	0.98	42.50	0.15
Leukocyte esterase (present or absent)	0.2	0.95	4.00	0.84
Leukocyte esterase + nitrite	0.5	0.98	25.00	0.51
Methylene blue	0.6	0.98	30.00	0.41
Uriscreen	0.9	0.9	9.00	0.11
Bac-T-Screen	0.9	0.7	3.00	0.14
Chemstrip LN	0.9	0.7	3.00	0.14

hpf high-power field, *WBC* white blood cell count
[a]5 WBCs/hpf + any bacteria in spun urinalysis
[b]10 WBCs/mm^3 + any bacteria by Gram stain

Table 2 Suggested culture colony count thresholds for significant bacteriuria

Various clinical settings	Significant bacteriuria (CFU/mL)
Infants and children	
Voided	$\geq 10^3$
Catheter	$\geq 10^3$
Suprapubic aspirate (SPA)	$\geq 10^3$
External collection devices	$\geq 10^4$
Adult	
Midstream, clean-catch	
Female	
Asymptomatic	$\geq 10^5$
Symptomatic	$\geq 10^2$
Male	$\geq 10^3$
In-and-out (straight) catheterization	$\geq 10^2$
Chronic indwelling catheter	$\geq 10^2$
Indwelling catheter or SPA in spinal injuries	Any detectable colony count
External collection devices	$\geq 10^5$
Condom collection device in spinal injuries	$\geq 10^4$

Sources: Data are from Cardenas and Hooton [35] and Eisenstadt and Washington [45]

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Fluid, Electrolyte, and Acid–Base Disorders

100

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Volume Overview

Volume distribution in the body is comprised of extracellular fluid and intracellular fluid. Most volume, approximately two-thirds, is found in the intracellular compartments. One-third is extracellular water, which accounts for extravascular (interstitial space) and intravascular. Water is able to cross membranes to freely move between compartments through aquaporin channels [1]. Thus,

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fluid distribution is dictated by effective solutes, largely sodium, to maintain osmolality via osmotic pressures. Given the kidney regulates sodium hemostasis, it is responsible for maintaining volume balance. In discussing volume status, it is important to remember that intravascular volume status, accounted for in our extracellular water hemostasis, is of most clinical significance.

Volume Depletion

Intravascular volume depletion can occur from actual volume loss or due to a fluid redistribution to another compartment, often the extravascular or interstitial compartment often clinically referred to as "third spacing." Actual volume loss occurs through various losses: hemorrhage, the gastrointestinal (GI) tract (i.e., poor intake, vomiting, diarrhea), kidneys (urination), and evaporation (through sweating and breathing). Relative volume loss results in decreased intravascular volume without a decrease of total fluid in the body. Third spacing refers to the redistribution of intravascular fluids to the interstitial space between skin and fascia, which is not normally perfused with fluids. Third spacing is commonly seen clinically as it can occur with increased fluid volume (fluid replacement, renal dysfunction), increased capillary hydrostatic pressure (CHF), decreased sodium level (due to sodium loss), lowered albumin (malnutrition, liver disease, protein-losing enteropathy), increased capillary permeability (burns, trauma, disseminated intravascular coagulation, infections), or lymphatic obstruction (iatrogenic removal).

Hypovolemia can be difficult to determine clinically, often requiring a thorough history and physical exam. In clinical scenarios of actual volume loss, patients can have clinical exam findings of hypovolemia including increased time to capillary refill, pallor of skin, dry mucous membranes, or positive orthostatic vital signs (i.e., postural blood pressure and pulse changes). However, volume status is particularly difficult to assess when patients appear fluid overloaded or edematous, but are instead intravascularly depleted, such as is seen in common clinical scenarios (e.g., congestive heart failure [CHF], cirrhosis, and nephrosis).

Laboratory data can often be helpful to determine fluid status in clinical cases where history and physical exam do not lead to obvious findings. Measurements such as serum osmolality (SOSM), blood urea nitrogen (BUN), urine osmolality (UOSM), urine specific gravity, kidney function, and blood counts can all be a part of your clinical evaluation. Signs of volume depletion include high urine specific gravity and UOSM (i.e., >1.015 and >350 mOsm/kg, respectively) as a result of ADH-induced renal water conservation leading to concentrated urine [1]. Renal hypoperfusion results in prerenal azotemia and functional renal injury causing BUN to be retained such that the normal 10:1 BUN/creatinine ratio is elevated (e.g., to >20:1) and may also lead to an increase in creatinine or decrease in GFR. When volume loss is due to hemorrhage, a hematocrit/hemoglobin can be low. However, hemoconcentration can occur with significant third spacing. Generally with hypovolemia, an increased SOSM, increased serum sodium, and corresponding decreased urine sodium (UNa) is seen; however, inappropriate responses can be seen with certain comorbidities.

Whether actual or relative, volume depletion results in decreased "effective circulating volume" (ECV) causing a cascade of multiple compensatory mechanisms. In response to a decreased ECV, cardiac and cerebral blood flow is compromised. Accordingly, cardiac and arterial baroreceptors sense the change in mean arterial pressure. This drop in mean arterial pressure triggers a norepinephrine-induced increase in heart rate and heart contractility with peripheral arterial vasoconstriction. Concurrently, decreased renal blood flow due to decreased ECV triggers antidiuretic hormone (ADH) release and activates the renin–angiotensin–aldosterone system (RAAS) [2].

Once activated, renal sodium is retained and vasoconstriction further promoted. ADH secretion contributes to vasoconstriction and decreased renal water clearance in an attempt to restore the

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ECV. Intrarenal prostaglandins are released with ADH stimulation and activation of RAAS. These prostaglandins blunt the hypovolemia-induced vasoconstriction in the renal vasculature, thereby disproportionately preserving renal blood flow and glomerular filtration. This physiological response to volume depletion is illustrated in Fig. 1. These vasoconstrictor mechanisms are triggered by volume depletion to protect cardiac and cerebral blood flow, while sacrificing blood flow to less critical organ systems [3].

Volume depletion is treated according to the clinical situation and etiology. Treatment for mild volume depletion occurs with slow restoration of the ECV such as using oral electrolyte solutions. Treatment escalates to infusion of isotonic fluid in more severe settings. In addition to replacing excess fluid loss, volume repletion must also include the replacement of daily obligate fluid losses. The rate of volume replacement depends on the clinical situation. Restoration of ECV results in normalization of orthostatic vital signs, improvement in tachycardia, and normalization of urinary excretion of sodium [3]. Once the volume status has been restored, treatment can be directed to restoring electrolyte loss and imbalances.

Volume Excess

Volume excess, or hypervolemia, can be caused by excessive fluid intake, excessive sodium intake, chronic hepatic or renal failure, steroid therapy, transfusion reaction, decreased cardiac output, head injury, medications, malnutrition, and mineralocorticoid excess. Volume overload can also be caused by decreased ECV, as discussed previously, which results in renal sodium and water conservation and edema formation (e.g., hypoalbuminemia and left ventricular dysfunction).

Total body volume excess caused by decreased ECV and edema formation may cause symptoms of vital organ hypoperfusion (e.g., syncope, unstable angina, decreased urine output, mental status changes). Depending on the etiology of volume excess, physical findings of CHF, hepatic cirrhosis, and nephrosis might be present. Weight gain may reflect the quantity of the volume retention, and monitoring weight gain can be clinically useful. Evidence of hypervolemia on exam could include edema, typically seen in the lower extremities or presacral area, pulmonary edema, elevated jugular venous pressure, or prolonged hepatojugular reflux in CHF [1]. However, exam findings of volume excess are not always evident, such as seen in a patient with anasarca or bowel wall edema. Hypervolemia associated with increased ECV causes urine sodium (UNa) wasting (UNa $>$20 mEq/L) and no excessive water retention (assuming normal osmolality).

Treating volume excess involves recognition and treatment of the underlying cause. For example, if caused by heart failure, increasing cardiac output. Furthermore, it would require restoring intravascular oncotic forces in patients with cirrhosis and hypoalbuminemia. Removal of some edema by loop diuretics may be required, especially if the retained fluid compromises ventilation. When third-spaced fluid is significant, it should be removed with caution, as removal of large amounts can cause rapid re-accumulations extracted from the circulating volume, resulting in hypotension [1]. With states of aldosterone excess, an aldosterone antagonist (i.e., spironolactone, eplerenone) is used to decrease sodium reabsorption and edema, but ideally the source of the hyperaldosteronism is removed. In renal failure, diuresis with potent loop diuretics may be required to remove excess volume that may be causing renal hypoperfusion, and in some cases, dialysis will be required to remove excess fluid in conjunction with a nephrology specialist.

Sodium Disorders

Appreciating a patient's fluid status is crucial when assessing and treating disorders of sodium concentration. Hyponatremia ($[Na^+] < 136$ mEq/L) and hypernatremia ($[Na^+] > 145$ mEq/L) should be approached in term of free water status. A firm understanding of tonicity is required when approaching sodium disorders.

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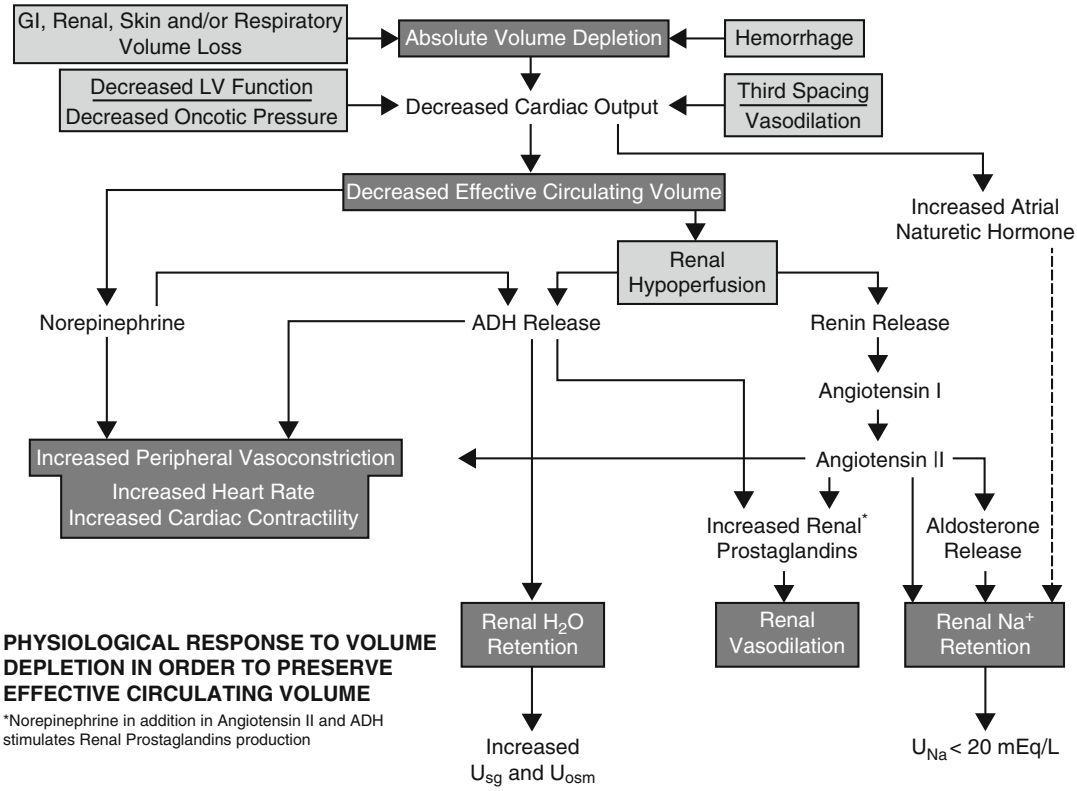


Fig. 1 Physiological response to volume depletion. *GI* gastrointestinal, *LV* left ventricle, U_{Na} urine sodium concentration, U_{osm} urine osmolality, U_{sg} urine specific gravity, *ADH* antidiuretic hormone, *SIADH* syndrome of inappropriate ADH secretion. (Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003)

Tonicity is the measure of the osmotic pressure gradient between the intracellular fluid compartment (ICF) and extracellular compartment (ECF). Tonicity is affected only by solutes that cannot cross a membrane while osmolality is the property of a particular solution. These compartmentalized solutes create an osmotic gradient across the cellular membrane [4]. Tonicity is the effective plasma osmolality with a normal range of 275–300 mOsm/kg H_2O. Only solutes that do not pass between the ECF and ICF contribute to creating osmotic gradients and effect the flow of water between the ECF and ICF. Sodium is a major plasma solute that cannot cross freely between the ECF and ICF, and is therefore important when evaluating plasma osmolality.

The plasma osmolality (POSM) is the total osmolality of the solutes in the plasma and can be calculated as:

$$P_{osm} = 2[Na^+] + \frac{[glucose]}{18} + \frac{[BUN]}{2.8}$$

Calculating the osmolality gap, the difference between effective POSM and measured osmolality can indicate the presence of unmeasured solutes that can be toxic such as ethanol, methanol, isopropanol, ethylene glycol, propylene glycol, or acetone. Therefore, evaluating plasma osmolality, effective and measured, would be the first step when approaching sodium disorders, with hyponatremia being the most common electrolyte abnormality [5]. Determining osmolality is also

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needed when approaching metabolic acidosis disorders which will be discussed later.

Hyponatremia

Hyponatremia is defined as $[Na^+] < 136$ mEq/L. Hypotonic, or hypoosmolar, hyponatremia (i.e., plasma osmolality <275 mOsm/kg) indicates excess water content relative to sodium caused by renal retention of ingested water such as hypovolemic-induced ADH release, SIADH, or excess water ingestion greater than renal free water clearance (Table 2). Pseudohyponatremia, which is hyponatremia with normal plasma osmolality between 275 and 300 mOsm/kg H_2O, occurs in the presence of severe hyperlipidemia, hyperproteinemia, or hyperglycemia as these cause relatively lower proportions of sodium in the plasma. When evaluating hyperglycemia, the correct sodium should be calculated [6].

Corrected sodium = Measured sodium +0.024 × (serum glucose – 100) [7]

Hyperglycemia causes an osmotic diuresis leading both to salt and water losses, total body volume depletion, or decreased renal perfusion.

Clinically, hypotonic hyponatremia can be further categorized by determining volume status [1]; there are three types of hyponatremia: hypovolemic, euvolemic, and hypervolemic. Common causes for hyponatremia are shown in Table 1.

Hypovolemic hyponatremia occurs in relation of solute to total body water, and sodium loss is mediated either by the kidneys or via extrarenal loss of sodium [4]. UNa concentration can be a helpful to measure to determine the etiology of hyponatremia, as UNa >20 mEq/L represents sodium loss through the kidneys [1].

Renal losses of sodium include diuretics, mineralocorticoid deficiency, cerebral salt wasting, salt wasting nephropathy, and renal tubular acidosis (RTA). Diuretic usage typically enhances urinary excretion of sodium-rich fluid by inhibiting sodium reabsorption in the nephron [1]. Mineralocorticoid deficiency from adrenal insufficiency leads to renal sodium wasting, causing a hypovolemic state and activating vasopressin to further concentrate urine sodium. Elevated serum potassium with hypovolemic hyponatremia should lead to further investigation of mineralocorticoid insufficiency. Cerebral salt wasting can occur after neurological surgery or head injury. A baroreceptor-mediated vasopressin release is activated by urine sodium and chloride loss, though etiology of this process is not well established [1, 2].

Medication side effects (beyond diuretic use) are another common cause of hyponatremia. Common medication classes associated with this

Table 1 Main causes of hyponatremia

Hypovolemic states	Euvolemic states	Hypervolemic states
Osmotic (e.g., glucosuria, bicarbonaturia, ketonuria)	Hypothyroidism	Congestive heart failure
Diuretics	SIADH (see Table 2)	Renal failure
Mineralocorticoid deficiency	Severe pain and/or stress	Cirrhosis
Salt-losing nephropathies	Glucocorticoid deficiency	Nephrosis
Cerebral salt wasting	Primary polydipsia	Decreased vascular integrity (e.g., sepsis, anaphylaxis)
GI volume losses (e.g., diarrhea, vomiting)	Beer potomania	Acute or chronic renal failure
Sweat losses	Dilute formula intake	
Third-space sequestration	Dilute tube feeding	

References used: [2]
ADH antidiuretic hormone, *GI* gastrointestinal, *SIADH* syndrome of inappropriate secretion of ADH, *ECV* effective circulating volume, UNa urine sodium concentration

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Table 2 Causes of syndrome of inappropriate antidiuretic hormone secretion

Central nervous system disorders causing increased hypothalamic production of antidiuretic hormone	***Ectopic production of antidiuretic hormone (e.g., bronchogenic carcinoma, oat cell carcinoma of the lung, pancreatic carcinoma)***
Infections (e.g., meningitis, HIV infection)	Pancreatic carcinoma
Vascular problems (e.g., subdural hemorrhage)	Prolactinoma
Primary and metastatic cancers	Others
Psychosis	Postoperative patient
Post pituitary surgery	Severe nausea
Hypothalamic infiltrative disease (e.g., sarcoidosis)	***Pulmonary disorders causing increased antidiuretic hormone production***
Others (e.g., Guillain-Barré syndrome)	Pneumonias
Pharmacologic agents	Tuberculosis
Stimulants of hypothalamic antidiuretic hormone secretion – haloperidol, amitriptyline, thioridazine, thiothixene, carbamazepine, fluoxetine and sertraline, monoamine oxidase inhibitors, and others	Acute respiratory failure
Potentiators of antidiuretic hormone effect – chlorpropamide, tolbutamide, carbamazepine	Others (e.g., asthma, pneumothorax)
Exogenous antidiuretic hormone preparations – vasopressin, oxytocin	

Adapted from: [2, 8]

change include proton pump inhibitors (PPIs), serotonin selection reuptake inhibitors (SSRIs), and antiepileptic medications. Although the mechanism is not clear for all medication classes, most often medication side effects leading to hyponatremia are related to SIADH or sodium-losing nephropathy [8].

Extrarenal losses leading to hypovolemic hyponatremia can be differentiated by a urine sodium concentration of <20 mEq/L and include GI losses (i.e., vomiting and diarrhea) and third-space sequestration (i.e., bowel obstruction, pancreatitis, peritonitis, ascites, massive tissue injury, venous congestion).

Euvolemic hyponatremia can be thought of as dilutional hyponatremia and is related to fluid intake above the kidneys' ability to excrete water (Table 1, Fig. 2) [5]. SIADH is the most common form of euvolemic hyponatremia (UNa usually >40 mEq/L) and occurs when excess ADH is secreted in the absence of volume or osmotic stimuli, resulting in water excess and hyponatremia. This can be caused by a variety of disorders including central nervous system and pulmonary diseases (Table 2). In addition, medications, hypothyroidism, and stress can all be common culprits of euvolemic hyponatremia [1].

Hypervolemic hyponatremia can commonly be seen with congestive heart failure (CHF), cirrhosis, nephrotic syndrome, and severe renal insufficiency are diseases that increase ECF volume through elevated ADH. Although total body sodium and water are increased in these states, the amount of water to sodium ratio is increased, leading to a lower sodium concentration. ADH secretion increases in left heart function and decreases due to baroreceptor mechanisms. If U[Na] > 20, this indicates an advanced renal disease such as acute or chronic renal failure. If U[Na] is low, this is more indicative of nonrenal causes such as congestive heart failure, cirrhosis, or nephrotic syndrome [1].

Symptoms of hyponatremia vary depending on the cause, severity, and rapidity of decline. Patients may be asymptomatic or mildly symptomatic with symptoms such as gait disturbance or mild cognitive deficits if hyponatremia is more chronic and less severe. However, if hyponatremia is more acute or sever, often below 125 mEq/L symptoms can be more profound. The spectrum of symptoms could range from mild headache, nausea, or confusion to severe features such as seizures, coma, or death [6].

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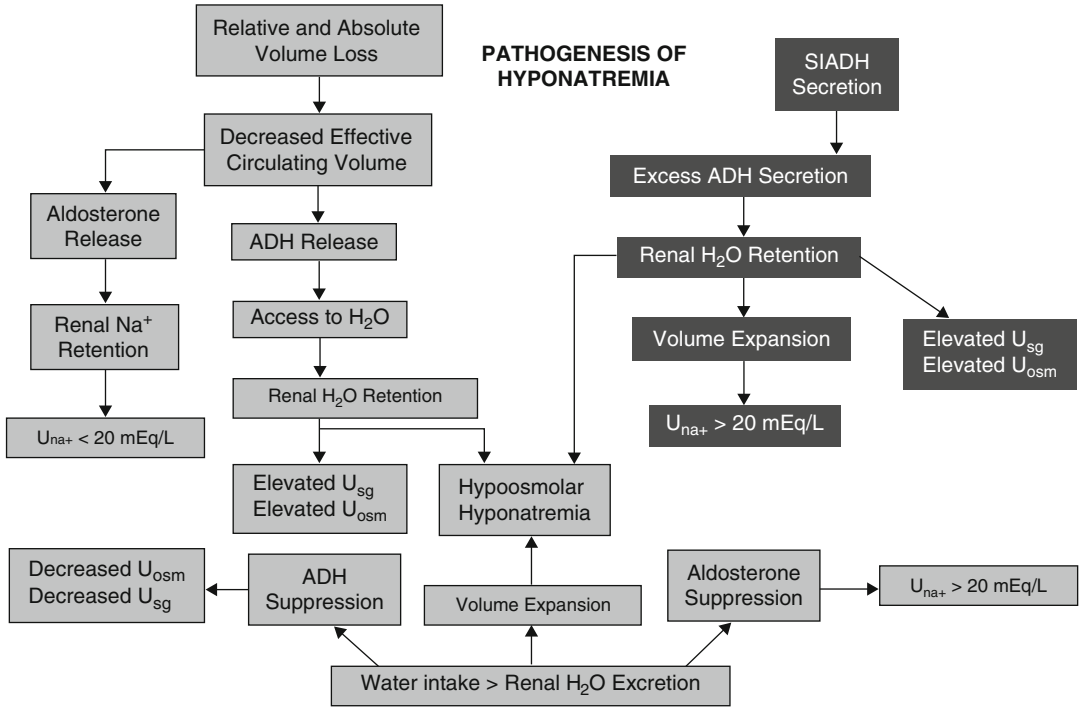


Fig. 2 Pathogenesis of hyponatremia. U_{Na} urine sodium concentration, U_{osm} urine osmolality, U_{sg} urine specific gravity, *ADH* antidiuretic hormone, *SIADH* syndrome of inappropriate ADH secretion. (Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003)

Treatment of hyponatremia is dependent on the expected cause. In hypotonic hypovolemic hyponatremia, sodium replacement should almost always be with oral or intravenous isotonic volume repletion. Both normal saline 0.9% (NS) and Lactated Ringer's Solution (LR) are considered isotonic. In NS, the sodium concentration is 154 mmol/L with an osmolarity of 286 mmol/kg. In LR, the sodium concentration is 130 mmol/L with an osmolarity of 273 mmol/kg. For patients with euvolemic hyponatremia, often caused by SIADH, re-equilibrating plasma osmolality is done via fluid restriction. Identifying and removing the source of SIADH secretion is also key. If hyponatremia cannot be corrected via fluid restriction and removal of inciting source in SIADH, oral tolvaptin can be considered [1]. In hypervolemic hyponatremia, the mainstay of treatment is at correcting the underlying condition, which is often done with diuretic therapy and fluid restriction [6]. In patients with severe hyponatremia symptomatic hyponatremia, infusion of hypertonic saline or hemodialysis can sometimes be required. Physicians comfortable with intensive or emergent medicine should direct this treatment. Goal of treatment in these cases is to restore ECV and normalize plasma osmolality. The sodium level should not be corrected more quickly than 9–12 mmol/L in the first 24 h [1].

Hypernatremia

Hypernatremia, serum sodium concentration > 145 mmol/L (Fig. 3), is caused by increased hypotonic fluid loss. Similar to hyponatremia, hypernatremia can occur in hypovolemic, euvolemic, or hypervolemic states [6]. Since hypernatremia is related to water status, thirst and access to water with an intact sensorium to drink when thirsty is crucial to not developing hypernatremia. However, excessive oral intake of

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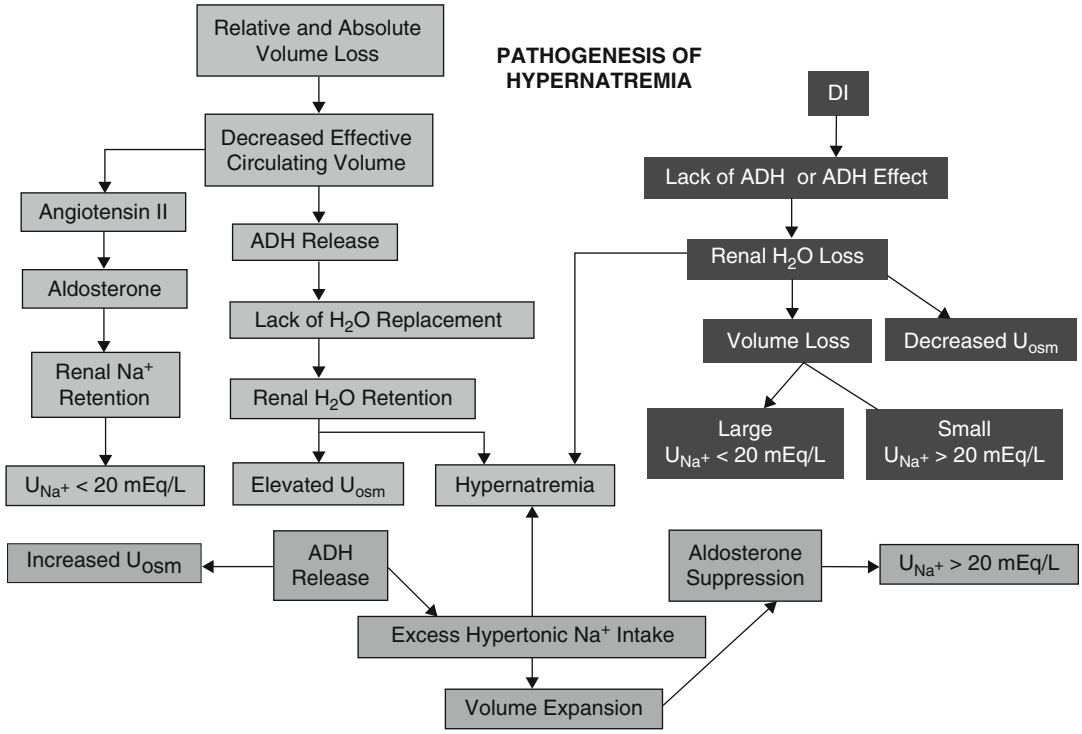


Fig. 3 Pathogenesis of hypernatremia. *DI* diabetes insipidus. (See Fig. 2 for other abbreviations). (Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003)

Table 3 Causes of hypernatremia

Causes	Examples
Primary hypodipsia (defect of thirst)	Primary or metastatic tumor, granulomatous disease, vascular disease, trauma
Diabetes insipidus	Central, nephrogenic
Pure hypertonic solute gain	Ingestion of hypertonic solutions, ingestion of salt tablets
Inadequate fluid intake with increased free water loss	Increase sweating, fever, GI losses, osmotic diuresis, diuretics

sodium salts and hypertonic volume expansion can also be a cause of hypernatremia [6, 9] (Table 3).

In hypernatremia, plasma osmolality is >300 mOsm/kg. Urine sodium concentration of <20 mEq/L can be seen in a hypernatremic patient with GI or insensible losses with inadequate hypotonic volume replacement. Additionally, high urine osmolality (e.g., >600 mOsm/kg) is observed in these patients as the kidneys attempt to maintain stable fluid and sodium balance through renal water conservation. When hypernatremia is caused by renal volume losses from diuretics or osmotic diuresis with inadequate hypotonic volume replacement, urine sodium concentration is >20 mEq/L, while urine osmolality may be <350 mOsm/kg and is less than plasma osmolality. With the addition of sodium salts for volume expansion, hypernatremia is associated with urine osmolality >350 mOsm/kg and urine sodium concentration > 20 mEq/L. Patients with severe hypernatremia (serum sodium concentration >155 mEq/L) without maximum concentrated urine (i.e., 800–1200 mOsm/kg)

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suggests diabetes insipidus, intrinsic renal disease, osmotic diuresis, or diuretic use [9, 10].

The symptoms of hypernatremia occur due to primarily to hypertonicity of ECF, which results in volume shifting out of cells. This primarily leads to neurologic symptoms ranging from confusion to coma depending on severity. Other clinically encountered neurologic disorders can include seizures, focal neurologic deficits, and intracerebral hemorrhage [1]. Polyuria can be seen depending on etiology of hypernatremia and reveal a renal loss of pure water (e.g., diabetes insipidus), osmotic diuresis (e.g., glycosuria), or diuretic use, especially in medications altering ADH function.

Treating hypernatremia depends on the cause. Correction of asymptomatic or chronic hypernatremia that develops over greater than 48 h or previously unknown hypernatremia must proceed slowly (i.e., [Na^+] reduction of 0.5 mEq/L/h) to avoid cerebral edema and resultant neurological dysfunction [11]. In cases when hypernatremia has developed in less than 48 h, or acute hypernatremia, correction can proceed at up to 1 mEq/L/h [11]. Hypernatremia correction that is too slow can also cause complications [12]. When ECV is diminished by hypotonic volume loss, volume expansion with isotonic saline is initially used until signs of hypovolemia have resolved. An added benefit of isotonic saline infusion is that it can contribute to equilibrating plasma osmolality in patients with hyperosmolality. Once euvolemia is re-established, hypotonic fluids (e.g., 0.45% normal saline or dextrose 5% in water [D_5W]) can be administered in order to decrease plasma osmolality in pure water losses from the skin or kidneys [12]. Hypernatremia caused by the addition of Na^+ salts is treated with D_5W and diuretics. Calculating free water deficit can be helpful for management; however, total body water and free water loss are grossly underestimated with the most commonly used equation: total body water deficit = correction factor x premorbid weight × (1–140/Na^+) [13]. Hypernatremia caused by diabetes insipidus is often treated with vasopressin (V2) agonists, such as desmopressin, with possible use of thiazide diuretics and a low sodium diet [6].

Potassium Disorders

Hypokalemia

Plasma potassium levels are typically maintained at 3.5–5.0 mmol/L, with hypokalemia described by potassium levels <3.5 mmol/L. Hypokalemia can be caused by a variety of nonrenal causes, where urine potassium (UK) <25 mEq/L, and due to renal causes with UK >25 mEq/L (e.g., sodium-losing nephropathies, mineralocorticoid excess, vomiting, diuretics, and hypomagnesemia) (Table 4). Hypokalemia is a common electrolyte abnormality that can be found, and is a common side effect of medications, such as non-potassium sparing diuretics.

Potassium is typically passively reabsorbed in the proximal tubule of the kidney with the movement of sodium and chloride, while being actively reabsorbed in the thick ascending loop of Henle in the medulla via Na-K-2Cl (NKCC2) cotransporter. Increased flow to the distal nephron that occurs in diuretics that are effective more proximally (e.g., loop and thiazide diuretics) lead to increased potassium loss. Additionally, volume depletion activates RAAS causing an increase in potassium excretion. In fact, anything that leads to increases in mineralocorticoid activity and subsequent aldosterone activity will also lead to renal potassium loss.

Aldosterone can directly increase the activity of the Na-K-ATPase pump, shifting potassium intracellularly. In addition, it can facilitate secretion of potassium into the tubular lumen. This can be seen in any condition or medication that leads to increased aldosteronism. If the amount of potassium transported to the distal lumen increases, it will lead to increased excretion. High urine output will also lead to increased potassium excretion. The increase in delivery of potassium to the distal lumen and the higher urine output are methods by which diuretic use can lead to low potassium. Metabolic alkalosis can also lead to an increase in potassium excretion [6].

Symptoms associated with hypokalemia can include generalized weakness, musculoskeletal complaints (muscle cramps, muscle tenderness), GI complaints (anorexia, nausea, vomiting,

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Table 4 Causes of hypokalemia

Renal potassium loss	Gastrointestinal loss	Intracellular K + sequestration	Pseudohypokalemia
Diuretics, current use	Diarrhea	Metabolic and respiratory alkalosis	Prolonged standing of collected blood with extremely high WBC count
Vomiting and nasogastric tube drainage	Excess sweating	Excess insulin	Blood specimen collected immediately after insulin administration
Magnesium depletion	Intestinal fistulas	Treatment of megaloblastic anemias	Decreased K+ intake
Mineralocorticoid excess (e.g., primary and secondary hyperaldosteronism, Cushing's disease, licorice ingestion, hyperreninism, Bartter syndrome, adrenal adenoma)	Rectal villous adenoma	Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Starvation
Diabetic ketoacidosis	Geophagia (i.e., clay ingestion)	β-adrenergic agonist	
Renal tubular acidosis	Laxative abuse	Hypothermia	
Ureterosigmoidostomy	Chloride-losing diarrhea	Catecholamine excess	
Polyuria		Hypokalemic periodic paralysis	
Osmotic diuresis			
Correction of chronic hypercapnia			

Adapted from Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003

constipation), polyuria, polydipsia, and cardiac complaints (palpitations, syncope). In skeletal muscle injury and rhabdomyolysis, potassium release from contracting skeletal muscle that would normally cause vasodilation and improved blood flow regionally is blunted in severe hypokalemia [14]. Potassium is also involved in cardiac muscle repolarization allowing for appropriate cardiac muscle relaxation and diastolic filling. With hypokalemia, cardiac repolarization is prolonged leading to classic electrocardiogram (EKG) changes. First noted is decreased magnitude of T waves, then U wave formation, and finally ST segment depression on EKG.

Oral replacement with potassium chloride or potassium bicarbonate and underlying correction of the cause are the mainstays of initial treatment. Oral therapy is less likely to have side effects and less likely to lead to over correction, and thus is the method of choice for repletion. However, intravenous repletion can be used for patient's unable to tolerate oral potassium, of it hypokalemia is severe (<3.0 mEq/L). Typically, 10 mEq of potassium supplementation will increase plasma potassium level by about 0.1 mEq/L. Potassium levels should be monitored every 2–3 h during repletion to avoid an overcorrection [6]. Low magnesium must be corrected to ensure potassium is not lost renally during repletion [15]. Diuretics that work in the distal convoluted tubule and antagonize aldosterone receptors (i.e.,spironolactone) can decrease urine excretion of potassium.

Hyperkalemia

Hyperkalemia (see Table 5) is less well tolerated by the body than hypokalemia and occurs when extracellular potassium levels are elevated beyond the ability of kidneys, skin, and GI tract to excrete

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Table 5 Causes of hyperkalemia

Increased K+ intake	Intracellular K+ extrusion	Measurement error
Dietary intake, medication intake	Metabolic and respiratory acidosis	Thrombocytosis
Decreased K+ excretion	Tissue injury (e.g., crush, rhabdomyolysis, hematoma resorption)	Leukocytosis
Acute and chronic renal failure	Insulin deficiency in diabetic ketoacidosis, prolonged fasting; hyperosmolality from hyperglycemia	Hemolysis of blood sample (i.e., delay after blood draw, cell destruction from vigorous sample shaking
Decreased effective circulating volume	Drugs (e.g., digitalis intoxication, succinylcholine, and arginine HCI, β-adrenergic blockers)	Blood collection from ischemic extremity
Hypoaldosteronism – K^+-sparing diuretics, hyporenin hypoaldosteronism in mild renal disease, NSAIDs, ACE inhibitors, adrenal insufficiency	Hyperkalemic periodic paralysis (from excessive exercise, fasting)	

References used [2, 19–22]

potassium. Extracellular potassium concentration can be affected by potassium shift from intracellular space to extracellular, potassium intake, and potassium excretion [16]. The kidneys perform most potassium excretion. Many medications can lead to hyperkalemia. Spironolactone, ACE-I, ARBs decrease aldosterone production, which can lead to hyperkalemia. Medications such as triamterene, amiloride, and the antibiotic trimethoprim decrease potassium excretion by blocking sodium channels. Other medications (e.g., nonselective beta-blockers, NSAIDs) can increase extracellular potassium by inhibiting Na-K ATPase pump, causing potassium to remain in extracellular fluid space and decreasing aldosterone production [17]. Avoiding a combination of these medications in patients with coexistent renal failure is important [17]. Kidney dysfunction (RTA type 4, CHF, and other causes of hypoaldosteronism) can inhibit potassium excretion [16].

Additional conditions and ingestions affect transcellular movement of potassium leading to hyperkalemia such as metabolic acidosis (0.2–1.7 mEq/L increase in $[K^+]$ for every 0.1 decrease in pH), hypertonicity from hyperglycemia or hypernatremia, insulin deficiency in diabetes mellitus or from starvation, rhabdomyolysis and hematoma resorption or other forms of cellular destruction, digitalis intoxication, and hyperkalemic periodic paralysis from intense exercise or fasting. Hyperkalemia due to measurement error is also quite common and can be caused by hemolysis of red blood cells as a result of collection (i.e., prolonged tourniquet use, fist clenching leading to minor ischemia) [18] or storage, release of K^+ during coagulation of blood samples with increased WBCs (e.g., WBCs $>100{,}000/mm^2$ in leukemia) (or increased platelets (i.e., $>1{,}000{,}000/mm^2$) [18–20].

Hyperkalemia can cause nonspecific symptoms such as muscle weakness, fatigue, malaise, nausea, vomiting, and paresthesias. Peaked T waves are hallmark EKG findings in hyperkalemia, though flattened P waves, increased PR interval, prolonged QRS duration with shortened QT interval may also be present. Uncorrected hyperkalemia can lead to sine wave development with resultant ventricular fibrillation and asystole. Bradycardia, dysrhythmias, and paralysis can also occur.

Treatment of acute hyperkalemia can be done by enhancing potassium cellular entry using insulin, glucose, and inhaled beta-agonists (i.e., albuterol or levalbuterol) [21]. If hyperkalemia is associated with life-threatening dysrhythmias, calcium is used to decrease the threshold of myocardial tissue excitability induced by hyperkalemia, thereby minimizing risk of serious cardiac events. Calcium chloride

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has more elemental calcium and greater bioavailability than calcium gluconate but is typically associated with tissue necrosis and therefore cannot be infused as rapidly; however, one salt has not been proven more effective over the other [22]. Sodium bicarbonate has not shown to be more effective than placebo [22]. Loop diuretics are effective for excreting total body potassium in patients who make urine and kayexalate. Sodium polystyrene was previously shown to be effective [16], but new data shows no difference compared to stool softeners alone and is associated with increased risk of intestinal necrosis [21, 23, 24]. In patients refractory to these treatments, hemodialysis may prove necessary [22].

Acid–Base Disorders

Normal acid–base status is defined as a pH 7.35–7.45. This homeostasis is maintained by renal and respiratory compensatory mechanisms. Acidosis is defined as pH <7.35. If the pH > 7.45, it would be an alkalosis. These abnormalities can either be metabolic, from renal dysfunction, or respiratory in nature.

Metabolic Acidosis

Metabolic acidosis is a primary reduction in plasma bicarbonate concentration leading to hypobicarbonatemia (Table 6), which stimulates compensatory hyperventilation and hypocapnia (i.e., decreased pCO_2). In metabolic acidosis, the compensatory hyperventilation can be determined with the following formula. Full compensation may take several hours.

$$\text{Calculation for expected } pCO_2$$
$$pCO_2 = 1.5 \times [HCO_3] + 8$$

The limit of compensatory hyperventilation in metabolic acidosis is 10 mmHg that may be more difficult to achieve in acute versus acute process. If the rate of the pCO_2 decrease is less or more than predicted, a mixed acid–base disturbance occurs [25–28]. If the actual pCO_2 is too high, then an additional respiratory acidosis is present; conversely, if the pCO_2 is too low, then an additional respiratory alkalosis is present.

The clinical scenario must be taken into account when approaching acid–base disorders. The etiology for the bicarbonate loss must be determined. Losses can occur with GI bicarbonate loss (e.g., diarrhea), renal bicarbonate loss (e.g., renal tubular acidosis), or bicarbonate titration with fixed endogenous acids (e.g., ketoacidosis) and exogenous acids (e.g., salicylate intoxication). Metabolic acidosis caused by pure bicarbonate loss is characterized by hyperchloremia and a normal anion gap. However, when metabolic acidosis is caused by the addition (e.g., methanol ingestion), retention (e.g., renal failure) [29], or excess production (e.g., lactic acidosis) of fixed acids that titrate bicarbonate, acidic anions remaining in extracellular body fluids cause expansion of the anion gap and a normal chloride concentration [30–32].

In reference to a calculated anion gap, a result of 20–30 has a high chance of metabolic acidosis, while a result >30 reflects metabolic acidosis. The anion gap is calculated using serum values with the following formula:

$$\text{Anion Gap} = [\text{Sodium}] \text{ -- } [\text{Chloride}] - [\text{HCO3}]$$

Metabolic acidosis can be divided into three categories: increased anion gap, normal anion gap, and decreased anion gap. Increased anion gap metabolic acidosis is caused by ingestion of organic acids (salicylates, methanol, ethylene glycol, paraldehyde, propylene glycol), increased organic acid production (lactic acidosis, ketoacidosis), renal failure (phosphates, sulfates), or errors of metabolism (lipid metabolism errors, urea cycle disorders). Normal anion gap metabolic acidosis is due to intake of chloride salts (total parental nutrition, normal saline infusion), GI bicarbonate loss (diarrhea, colostomy, ileostomy, enteric fistula), urological procedures (ureterosigmoidostomy, ureteroileal conduit), ingestions (acetazolamide, magnesium sulfate), and renal bicarbonate loss (RTA, tubulointerstitial renal disease, hyperparathyroidism).

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Table 6 Causes of hypobicarbonatemia[a]

Hyperchloremia, normal anion gap	Normochloremia, large anion gap (urine pH < 5.5)	Increased CNS stimulation
Bicarbonate loss (hypokalemia and urine pH < 5.5)	Excessive production of endogenously generated organic acids	Physiologic and psychogenic hyperventilation
GI tract bicarbonate loss (e.g., diarrhea, ureterosigmoidostomy, fistulas, tube drainage)	Diabetic ketoacidosis (i.e., excessive β-hydroxybutyrate and acetoacetate)	CNS disease (e.g., infectious, trauma, infarct, bleeding, tumors, heat stroke)
Renal bicarbonate loss and production failure (e.g., RTA type 2, RTA type 1, RTA type 4, carbonic anhydrase inhibitors)	Starvation ketosis	Pregnancy
HCl addition (e.g., NH_3Cl and some hyperalimentation fluids)	Alcoholic ketosis	Progesterone-producing tumors
Hypoaldosteronism (hyperkalemia, submaximal urinary acidification)	Lactic acidosis	Hepatic encephalopathy
Primary adrenal insufficiency	Muscle necrosis	Methylxanthines, nicotine, salicylates
Hyporeninemic hypoaldosteronism (e.g., during early chronic renal failure, acute renal failure interstitial nephritis, angiotensin-converting enzyme inhibition, and nonsteroidal anti-inflammatory drug use)	Decreased excretion of endogenous acid metabolites	Sepsis
Aldosterone resistance (e.g., spironolactone, amiloride, triamterene)	Renal failure	Hypoxia
Intestinal nephritis	Ingestion of exogenous agents causing organic acidosis	High altitude
Early renal failure	Methanol	Anemia, severe
Acute renal failure	Ethylene glycol	
Initial recovery from organic acidosis (variable $[K^+]$ and urine pH)	Paraldehyde	
	Salicylates	
	Respiratory alkalosis (i.e., increased pH, decreased $[HCO_3^-]$[c] and decreased pCO_2[b])	

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[a]Hypobicarbonatemia = decreased $[HCO_3^-]$

[b]Primary acid–base event

[c]Secondary or compensatory acid–base event

Metabolic acidosis causes extracellular hyperkalemia due to cellular buffering of hydrogen ions (failure of acidosis-induced hyperkalemia suggests total body potassium depletion), but because significant volume loss is a frequent complication (e.g., diabetic ketoacidosis), total body hypokalemia must always be expected (chronic renal failure and hypoaldosteronism may be an exception) [18]. The ingestion of acid toxins (e.g., paraldehyde, methanol, ethylene glycol, and salicylates) is associated not only with the distinct acid metabolite but also lactic acid as vascular collapse ensues [33].

Generally, compensatory responses will not be able to restore pH back to the normal value. Some of the most dangerous effects of acidosis on the body include hyperventilation, depression of myocardial contractility, sympathetic over activity, peripheral arteriolar vasodilation, hyperkalemia, and cerebral vasodilation with resultant increased intracranial pressure. Many of these conditions can be deleterious and deadly. Therapy

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for metabolic acidosis is initially directed at restoration of the systemic pH to levels that do not compromise cardiac function or predispose to cardiac dysrhythmias. Dangerous pH levels differ depending on the etiology of the acidosis; in general, however, safe systemic pH exists at 7.2. The use of sodium bicarbonate to increase pH has been controversial. Although useful in disorders associated with sodium loss, such as diarrhea or rental tubular acidosis, it has not been proven to be useful in all clinical setting. Specifically, it has not improved outcomes or mortality in common causes of metabolic acidosis, such as sepsis, lactic acidosis, and diabetic ketoacidosis [89]. Severe forms of metabolic acidosis requiring administration of sodium bicarbonate should be undertaken with care taken to avoid volume excess and post-treatment metabolic alkalosis by overaggressive alkali therapy [34]. If the metabolic acidosis is severe enough to warrant consideration of alkali therapy, a specialist consult would be warranted [33, 34].

Metabolic Alkalosis

Metabolic alkalosis is a primary increase in plasma bicarbonate concentration (i.e., hyperbicarbonatemia) that causes a compensatory reduction in ventilation and relative hypercapnia (i.e., increased pCO_2) [2]. The bicarbonate accumulation is due to acid loss, alkali administration, intracellular shifts, or bicarbonate retention. With primary metabolic alkalosis, the compensatory hypoventilation occurs at a rate of 0.7 mmHg increase in the pCO_2 for every 1.0 mEq/L increase in the bicarbonate concentration. The limit of this compensatory hypoventilation is 55 mmHg because of hypoxia-induced ventilation. If the rate of pCO_2 increase is less or more than predicted, a mixed acid–base disturbance consisting of metabolic alkalosis and respiratory alkalosis or acidosis is present. The list of potential causes for metabolic alkalosis is extensive, but most common reasons include loss of gastric acid, renal acid loss, hypovolemia, hypokalemia, and diuretic use (Table 7).

Signs and symptoms associated with metabolic alkalosis relate to underlying cause. Metabolic alkalosis caused by volume depletion is characterized by a urinary chloride concentration of less than 10 mEq/L (i.e., saline-responsive), whereas metabolic alkalosis due to a primary increase in distal renal tubule activity (e.g., mineralocorticoid excess) and increased alkali ingestion is characterized by a urinary chloride concentration higher than 10 mEq/L (i.e., saline-resistant). Paradoxically, the urinary pH is usually acidic except when the disorder is caused by excessive alkali ingestion.

Treatment of saline-responsive metabolic alkalosis requires volume repletion with isotonic normal saline, which inhibits the volume depletion-induced retention of bicarbonate, resulting in an alkaline diuresis. With saline-resistant metabolic alkalosis, the source of the excess alkali ingestion must be removed or inhibited. Potassium deficits should also be replete using potassium chloride.

Respiratory Acidosis

Respiratory acidosis is a primary increase in the pCO_2 (i.e., hypercapnia), which stimulates compensatory cellular and renal retention of bicarbonate [2]. With primary acute and chronic respiratory acidosis, the compensatory bicarbonate retention occurs at a rate of 1.0 mEq/L or 4.0 mEq/L for every 10 mmHg increase in the pCO_2. The limits of the metabolic compensations during acute and chronic respiratory acidosis are 30 and 45 mEq/L, respectively. If the rate of compensatory bicarbonate retention is less or more than predicted, a mixed acid–base disturbance consisting of respiratory acidosis and metabolic acidosis or alkalosis is present. Respiratory acidosis occurs through three mechanisms: (1) excess CO_2 in the inhaled gas, (2) decreased alveolar ventilation, and (3) increased production of CO_2. The most likely cause is inadequate alveolar ventilation. A list of etiologies is provided in Table 7.

Symptoms of respiratory acidosis include shortness of breath and the mental status changes associated with progressive acute and chronic

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Table 7 Causes of hyperbicarbonatemia[a]

Acid–base disorder	Etiology	Example
Metabolic alkalosis (i.e., increased $[HCO_3^-]$[b], increased pCO_2, increased pH)	Hypervolemia (i.e., hypochloremia, hypokalemia; urine $Na^+ > 10$ mEq/L, $Cl^- > 10$ mEq/L, pH < 6.0)	Mineralocorticoid excess, renal artery stenosis, primary aldosteronism, adrenal hyperplasia
	Hypovolemia and chloride depletion (i.e., hypochloremia, hypokalemia: urine $Na^+ < 10$ mEq/L, $Cl^- < 10$ mEq/L, pH < 6, $K^+ < 10$ mEq/L	Vomiting, post-diuretic use, congenital chloride diarrhea, Bartter syndrome, acute correction of hypercapnia in hypovolemia
	Excessive alkali (hypochloremia, hypokalemia; urine $Na^+ > 10$ mEq/L, $Cl^- > 10$ mEq/L, pH > 7.0)	Excessive exogenous alkali (e.g., absorbable antacids, milk-alkali syndrome, excessive infusion of $NaHCO_3$), excessive endogenous alkali ($NaHCO_3$), acute correction of chronic hypercapnia in euvolemia, metabolism of β-hydroxybutyrate, acetoacetate, lactate, and citrate
	Severe hypokalemia	
	Hypercalcemia (e.g., primary hyperparathyroidism)	
Respiratory acidosis (i.e., lactate, increased pCO_2,[b] increased $[HCO_3^-]$	Suppression of CNS respiratory center	Oxygen-induced acute pCO_2 retention in chronic obstructive pulmonary disease (COPD), sedating medications, sleep apnea
	Disorders of respiratory muscles	
	Obstructed airway	Laryngeal edema or spasm, extrinsic foreign body, aspiration, bronchospasm
	Disturbances of gas exchange across alveolar membrane	Pulmonary edema, adult respiratory distress syndrome, diffuse pneumonia, COPD
	Loss of ventilatory volume	Hemothorax, pneumothorax, pleural effusions

Originally appeared in: Taylor R, David A, Fields S, Phillips M, Scherger J, editors. Family medicine (Taylor). New York: Springer; 2003

[a]Hyperbicarbonatemia = increased $[HCO_3^-]$

[b]Primary acid–base event

hypercapnia. The treatment of respiratory acidosis is directed to the primary cause to increase the effectiveness of ventilation and pulmonary gas exchange.

Respiratory Alkalosis

Respiratory alkalosis is a primary reduction in the pCO_2 (i.e., hypocapnia), which stimulates a compensatory cellular and renal reduction in bicarbonate concentration [2]. With primary acute and chronic respiratory alkalosis, the compensatory bicarbonate loss occurs at a rate of 2.0 mEq/L or 5.0 mEq/L for every 10 mmHg decrease in the pCO_2. The limits of these metabolic compensations in acute and chronic respiratory alkalosis are 18 and 12 mEq/L, respectively. If the rate of compensatory bicarbonate loss is less or more than predicted, a mixed acid–base disturbance is present which is discussed later. Respiratory alkalosis is caused by central causes, hypoxia, pulmonary causes, and iatrogenically (excessive controlled ventilation) (Table 6).

Acute hypocapnia may be associated with circumoral and digital paresthesias, lightheadedness, carpopedal spasm, and tetany. The associated hyperventilation is obvious, as it is mostly rate driven. With chronic hypocapnia, the respiratory rate may be normal, and the depth of

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respiration may predominate as the mechanism of pCO_2 removal. Treatment is directed to the underlying cause.

Mixed Acid–Base Disturbances

The presence of a mixed acid–base disturbance is usually detected when a primary acid–base event fails to demonstrate the expected compensation. This failure of compensation can predict the presence of a respiratory and metabolic acid–base event occurring concurrently but does not predict the presence of mixed metabolic events or mixed respiratory events. Acid–base maps have similar diagnostic limitations. The mixture of more than two events can be determined by other laboratory evidence but is best detected when historical evaluations suggest multiple acid–base events. Although laboratory data may be the first evidence of acid–base disturbances, utilization of these tools to predict primary and mixed acid–base disturbances must be related with clinical data to ensure that the information is appropriately interpreted (Table 8).

The presence of a mixed acid–base disturbance is best detected by anticipating its presence in clinical settings, although some laboratory findings can be helpful. The compensation in acid–base disturbances minimizes changes in systemic pH but never totally corrects the pH (the possible exception is chronic hypocapnia in persons living at high altitudes). Therefore, the presence of a normal pH with normal $[HCO_3^-]$ and pCO_2 indicates the presence of a mixed acid–base disturbance. Likewise, with primary acid–base

Table 8 Common mixed acid–base disturbances

Disorder	Examples
Predicted by rules of compensation	
Metabolic acidosis and respiratory alkalosis (partial pressure of carbon dioxide reduction greater than predicted for metabolic acidosis)	Chronic renal failure and septicemia
Metabolic alkalosis and respiratory acidosis (partial pressure of carbon dioxide reduction less than predicted for metabolic acidosis)	Lactic acidosis and chronic obstructive pulmonary disease
Metabolic and respiratory alkalosis (partial pressure of carbon dioxide elevation less than predicted for metabolic alkalosis)	Diuretic overuse and psychogenic hyperventilation
Metabolic alkalosis and respiratory acidosis (partial pressure of carbon dioxide elevation greater than predicted for metabolic alkalosis)	Vomiting and adult respiratory distress syndrome
Not predicted by rules of compensation	
Hyperchloremia and large anion gap metabolic acidosis (nonequivalent changes in chloride and bicarbonate concentrations and an elevated anion gap	Diarrhea and chronic renal disease
Metabolic alkalosis and large anion gap acidosis (nonequivalent changes in chloride bicarbonate concentrations and an elevated anion gap)	Vomiting and chronic renal failure
Acute and chronic respiratory alkalosis ($[HCO_3^-]$ reduction greater than predicted for acute respiratory alkalosis and less than predicted for chronic respiratory alkalosis)	Septicemia and psychogenic hyperventilation
Acute and chronic respiratory acidosis ($[HCO_3^-]$ elevation greater than predicted for acute respiratory acidosis and less than predicted for chronic respiratory acidosis)	Acute respiratory failure and COPD
Chronic respiratory acidosis and acute respiratory alkalosis ($[HCO_3^-]$ elevation or reduction inconsistent with expected pCO_2 elevation or reduction for either of these disorders, respectively)	COPD and pulmonary embolus
Metabolic alkalosis and nonanion gap metabolic acidosis (difficult to recognize because $[Cl^-]$ and $[HCO_3^-]$ changes depend on which disorder predominates; if each disorder is of equal magnitude, then $[Cl^-]$, $[HCO_3^-]$, pCO_2, and pH are normal)	Chronic diuretic overuse and diarrhea

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COPD chronic obstructive pulmonary disease

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disturbances, the compensatory event is in the same direction as the primary event; therefore, acid–base disturbances where the compensatory event and the primary event are in opposite directions also indicate the presence of a mixed acid–base disturbance. A large anion gap metabolic acidosis occurring concurrently with a hyperchloremia metabolic acidosis (e.g., a patient with diabetic ketoacidosis and diarrhea) is detected when the anion gap does not account for the amount of $[HCO_3^-]$ concentration reduction. An example of this mixed disturbance is a sign of recovery during the appropriate treatment of diabetic ketoacidosis as β-hydroxybutyrate and acetoacetate (ketone bodies) are hepatically converted to $[HCO_3^-]$, resulting in a transition from the original large anion gap metabolic acidosis to a hyperchloremia metabolic acidosis with less severe systemic pH reductions. The presence of a large anion gap, regardless of the systemic pH, indicates the presence of metabolic acidosis. For example, a patient with plasma metabolic alkalosis caused by diuretic use may have a $[HCO_3^-]$ of 36 mEq/L, and if the hypovolemia becomes severe enough, lactic acidosis may ensue. However, an 8 mEq/L drop in $[HCO_3^-]$ caused by titration of lactic acid would result in a $[HCO_3^-]$ of 28 mEq/L, essentially no change in $[Cl^-]$, and an appropriate pCO_2 response with the pH still slightly alkalemic. This process can be detected early based on the concurrent increase in the anion gap as $[HCO_3^-]$ is consumed in the titration with lactic acid and elevated plasma lactic acid – if the potential for this disorder had been anticipated clinically.

The limits of compensation are important factors to consider especially when suspecting respiratory acidosis in a patient with metabolic alkalosis. Although the compensation for metabolic alkalosis is pCO_2 retention, pCO_2 values higher than 55 mmHg do not occur because the resulting hypoxia stimulates ventilation. Therefore, in patients with metabolic alkalosis and a pCO_2 higher than 55 mmHg, primary impairment of ventilation causing respiratory acidosis must also be present. Because the limits of compensation in chronic respiratory alkalosis is a $[HCO_3^-]$ of 14 mEq/L, $[HCO_3^-]$ less than that implies the additional presence of metabolic acidosis. Likewise, the limits of compensation for chronic respiratory acidosis is renal HCO_3 retention to 45 mEq/L, and higher $[HCO_3^-]$ concentrations imply the additional presence of metabolic alkalosis. Because chronic renal disease in its end stages results in a $[HCO_3^-]$ of 12–14 mEq/L, greater $[HCO_3^-]$ reductions would suggest additional causes of metabolic acidosis (e.g., vomiting).

Mixtures of acute and chronic respiratory acidosis as well as acute and chronic respiratory alkalosis can be detected using the rules of compensation for primary acid–base disorders and by plotting pCO_2 and $[HCO_3^-]$ on acid–base maps. Points that define mixtures of acute and chronic respiratory alkalosis or respiratory acidosis may also be consistent with a mixture of acute respiratory and metabolic alkalosis or acute respiratory acidosis and metabolic alkalosis. Mixtures of respiratory acidosis and respiratory alkalosis pose special problems. The more profound event may alter the pCO_2 enough to leave the respiratory-induced metabolic compensation unopposed for hours to days (e.g., a patient with chronic obstructive pulmonary disease who is mechanically hyperventilated, thereby decreasing the pCO_2 and leaving the pCO_2-induced $[HCO_3^-]$ elevation until renal $[HCO_3^-]$ excretion occurs over the following hours to days).

Miscellaneous Electrolyte Disturbances

Magnesium

Hypomagnesemia ($Mg^{2+} < 1.5$ mEq/L) associated with urinary magnesium (UMg) conservation (UMg < 10 mg/day) can be caused by decreased magnesium intake (e.g., protein calorie malnutrition), decreased magnesium absorption, and extrarenal magnesium loss [2]. Hypomagnesemia associated with urinary magnesium excretion (UMg > 10 mg/day) can be caused by excessive renal magnesium loss (e.g., diuretic use, hypokalemia, hypercalciuria, hypervolemia, and hyperthyroidism). Hypomagnesemia is also caused by chronic magnesium wasting and treatment-induced

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intracellular magnesium redistribution (e.g., diabetic ketoacidosis and alcoholism). Hypomagensium is commonly seen concurrently with hypokalemia. In these instances, it is best to replete magnesium prior to repleting potassium, as hypomagnesemia can lead to renal potassium wasting [1].

Hypermagnesemia is often transient and related to increased dietary magnesium intake. However, the kidney has a large capacity to excrete magnesium. When hypermagnesemia is persistent, it is most often due to chronic renal insufficiency in conjunction with taking excessive amounts of magnesium medications or supplementation. When magnesium reaches levels above 4-6 mg/dL, it can be toxic and lead to grave effects including hypotension, urinary retention, and ileus. At levels above 8–12 mg/dL, hyporeflexia, paralysis, bradyarrythemias, and death from respiratory depression or cardiac arrest is possible [1].

Phosphate

Hypophosphatemia (plasma phosphorus <2.5 mg/dL) is caused by increased phosphate renal excretion (i.e., UPO4 > 100 mg/24 h) in diabetic ketoacidosis, hypokalemia, and phosphate deficiency (UPO4 < 100 mg/24 h) in hypoparathyroidism and decreased phosphate intake (e.g., alcoholism, vitamin D deficiency, and use of phosphate binders), as well as intracellular phosphate shifts (UPO4 < 100 mg/24 h) in metabolic and respiratory alkalosis [2]. Hyperphosphatemia (phosphorus >4.8 mg/dL) associated with UPO4 > 1500 mg/24 h is caused by increased release of phosphates into the extracellular fluid by cell lysis (e.g., rhabdomyolysis) and initial anionic redistribution of metabolic acidosis (e.g., diabetic ketoacidosis and lactic acidosis).

Hyperphosphatemia associated with UPO4 < 1500 mg/24 h is caused by decreased renal phosphate excretion (e.g., volume depletion, acute and chronic renal failure, and hyperparathyroidism). Clinical manifestations vary depending on time course and mechanism. Symptom presentation is more severe with acute versus chronic. Symptoms may be mild if from intracellular shift as intracellular phosphate levels are enough for ATP production. Clinically patients may develop respiratory muscle dysfunction, decreased contractility of heart, hemolysis, insulin resistance, myopathy, rhabdomyolysis, and seizures. These symptoms are largely caused by adenosine triphosphate depletion in hypophosphatemia. Treatment is phosphate repletion and may be done either orally or intravenously.

Calcium

Hypocalcemia (Ca^{2+} < 8.5 mg/dL or ionized Ca^{2+} < 4.1 mg/dL) associated with normal or subnormal parathyroid hormone (PTH) is caused by PTH-deficient hypoparathyroidism and severe hypomagnesemia. Since 40% of Ca is bound to plasma proteins, it is important to adjust for low albumin by adding 0.8 mg/dL for every 10 g/L decrease in normal albumin [1]. Calcium is regulated by parathyroid hormone. When levels of Ca^{2+} are low, PTH is secreted from the parathyroid resulting in increased renal reabsorption as well as increased renal vitamin D production, which stimulates increased intestinal absorption of calcium. Hypocalcemia associated with elevated PTH is caused by chronic renal failure, vitamin D deficiency, malabsorption, drug-induced microsomal enzyme induction (e.g., mithramycin and phenytoin), osteomalacia, and causes of severe acute hyperphosphatemia such as acute pancreatitis, hepatic failure, and other causes of massive tissue necrosis.

Hypercalcemia (total [Ca^{2+}] > 10.5 mg/DL or ionized [Ca^{2+}] > 5.1) with elevated PTH is caused by primary hyperparathyroidism (i.e., excessive production of PTH) and severe secondary hyperparathyroidism of chronic renal failure. Hypercalcemia associated with normal PTH is caused by vitamin D excess, sarcoidosis, hyperthyroidism, increased bone calcium release (e.g., immobilization and bony metastasis), extracellular fluid depletion, thiazides, or milk-alkali syndrome. Clinical manifestations include nephrolithiasis, bone pain, abdominal pain from constipation, nausea, vomiting, and psychiatric symptoms. Asymptomatic patients with mild hypercalcemia do not need treatment; however, if >14 mg/DL or if >12 mg/DL with symptoms should be treated with aggressive saline

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rehydration followed by furosemide diuresis, calcitonin, and bisphosphonates. Surgery would be indicated for primary hyperparathyroidism.

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Diseases of the Kidney

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Glomerulonephritis

The nephritic syndrome is acute in onset and associated with oliguria, azotemia, hypertension, and proteinuria of variable quantity. Hematuria (usually dysmorphic) and RBC casts are the hallmark of glomerular inflammation and glomerular basement membrane disruption. A diverse group of diseases cause the syndrome and the presentation is often dramatic and can be life threatening.

Acute Proliferative Glomerulonephritis/Poststreptococcal Glomerulonephritis

This condition is characterized by diffuse proliferation within the glomerulus and the prototypical disease is poststreptococcal glomerulonephritis. The disease occurs 1–2 weeks after a skin infection or sore throat and may occur in as many as 25% of patients affected by Group A streptococci, M-type stains [1, 5, 13]. The condition usually develops in children but can occur at any age. Serum complement is typically low; antistreptolysin O and DNAase B titers are high. These patients usually have a dramatic presentation with nephrotic syndrome, gross hematuria with dark and smoky urine, RBC casts, hypertension, and acute kidney failure. Milder manifestations with non-nephrotic proteinuria and microscopic hematuria without renal failure can also be seen. Most patients recover spontaneously although persistent urinary abnormalities may persist and a small subset of patients may develop chronic kidney disease (CKD) [1, 2].

Immunoglobulin A Nephropathy

IgA nephropathy is the most common form of glomerulonephritis worldwide. IgG-IgA1 immune complexes are deposited in the mesangium of the glomerulus and incite an inflammatory reaction. IgA levels in the blood do not correlate with disease although the pathogenesis may involve a decrease in galactosylation of IgA1 making it susceptible to an antibody response. Primary care physicians are often the first providers who evaluate these patients for gross hematuria following an upper respiratory infection in adolescence or as young adults. Although the condition is often benign, a more aggressive form of the disease can occur which can lead to End-Stage Kidney Disease (ESKD). IgA nephropathy often accompanies Henoch-Schönlein purpura which is a condition appearing earlier in life (mean age 6–7 years) and associated with a purpuric rash usually involving the legs and buttocks, abdominal pain, arthritis and arthralgias. The condition, including IgA nephropathy, usually resolves spontaneously with conservative management. IgA deposits with or without associated nephropathy can

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accompany a variety of diseases including sarcoidosis, HIV infection, liver disease, and inflammatory bowel disease. The significance of these deposits remains unclear. Therapy for typical IgA nephropathy includes omega-3-fatty acids and/or angiotensin-converting enzyme inhibitors, both of which have shown promise in slowing the progression of disease; glucocorticoids may be of benefit in the setting of persistent proteinuria [3].

Lupus Nephritis

Patients with systemic lupus erythematosus commonly have renal involvement, although the extent of involvement is highly variable. Lupus nephritis is an immune complex mediated glomerular disease with autoantibodies to a variety of antigens (nuclear, double-stranded DNA). These autoantibodies are deposited in the glomerulus, activate complement and elicit an inflammatory response that damages the kidney. Six histologically distinct classes of renal involvement have been described with class 4, diffuse proliferative glomerulonephritis being the most severe. It is not uncommon for glomerular histology to change in a single patient necessitating very close follow-up. Besides following renal function and urinalysis, complement activity and anti-double-stranded DNA titers fluctuate with disease activity. Therapy is best described for class 4 diffuse proliferative lupus nephritis. Treatment with high doses of intravenous and oral steroids and intravenous or oral cyclophosphamide have been successfully employed. Oral mycophenolate mofetil has been shown to be equally effective and has fewer side effects. Recently, intravenous rituximab has also been used as a second-line agent [4].

Rapidly Progressive Glomerulonephritis (RPGN)

RPGN, also known as crescentic glomerulonephritis, is a dramatic condition causing a rapid, often irreversible, decline in renal function. Prompt diagnosis is required, if left untreated it uniformly leads to ESKD or death. Crescents are cellular elements that follow the contour of Bowman's capsule, crowding out the capillary loops in the glomerulus. Crescents are not specific to any particular type of RPGN but the extent of their presence (>60% glomerular involvement) denotes the severity of the inflammatory response within the glomerulus. There are three types of RPGN based on distinct pathogenic mechanisms.

Type 1 RPGN

Although rare, this type of RPGN is often the best known of the types of RPGN. It is known as anti-GBM disease when the disorder is confined to the kidney, but if there is cross-reactivity to alveolar basement membrane leading to pulmonary hemorrhage it is known as Goodpasture syndrome. Early initiation of therapy is critical in this disorder in order to prevent ESRD. Anti-GBM antibody titers can be followed to monitor therapeutic effectiveness, but results are often delayed; for more expedient results a kidney biopsy is often required. Intravenous steroids, cyclophosphamide, and plasmapheresis are usually effective in improving renal function and controlling pulmonary hemorrhage if used early in the course of the disease. As this is an antibody mediated disorder, use of the anti-CD20 agent, rituximab, has also shown promise in controlling the disorder. In most instances, maintenance therapy with cyclophosphamide, mycophenolate mofetil, or azathioprine is necessary to control the disease [5].

Type 2 RPGN

Type 2 RPGN can be produced by any immune complex–mediated glomerulonephritis. The immune complexes can be virtually anywhere within the glomerular structure: mesangial, subendothelial, intramembranous, or subepithelial. The presence of crescents is a result of the intense inflammatory response. Although IgA nephropathy is usually a benign glomerular disease, it can present as Type 2 RPGN leading to ESKD. Therapy consists of intravenous steroids and cytotoxic drugs with less reliance on plasmapheresis.

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Again, early initiation of therapy is critical if ESKD is to be avoided.

Type 3 RPGN

Type 3 RPGN is also known as pauci-immune complex glomerulonephritis owing to the lack of immune complexes demonstrated in the glomerulus. However, circulating antineutrophil cytoplasmic antibodies (ANCA) are usually present and are thought to be critical in the pathogenesis of the disease. Most of these patients will have an underlying small vessel vasculitis such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), or eosinophilic granulomatosis with polyangiitis (EGPA). Asthma is frequently the most prominent symptom, but these disorders often affect multiple organ systems simultaneously. Flu-like symptoms often occur for weeks in affected individuals. Rash (usually purpuric), arthralgias, symptoms of a peripheral neuropathy, and nonspecific pulmonary symptoms including pulmonary hemorrhage and chronic sinusitis may be present. Eosinophilia is usually present but not specific for EGPA. With MPA and GPA circulating ANCA is usually present. Two major classes of ANCA are reported. Antibodies with a cytoplasmic pattern of staining, c-ANCA, are directed toward proteinase-3 whereas antibodies with perinuclear staining, p-ANCA, are directed toward myeloperoxidase. Over 75% of patients will have some pattern of positive ANCA with c-ANCA being more common with GPA and p-ANCA positive in MPA. There is considerable overlap in ANCA patterns, however, with some patients even demonstrating a negative ANCA or positivity to both c- and p-ANCA. As with the other types of RPGN, early diagnosis and therapy is essential in order to avoid ESKD. Dramatic response to intravenous steroids and cyclophosphamide is often seen, with an overall response rate exceeding 90%. For patients with aggressive pulmonary disease, plasmapheresis should also be employed. Rituximab has also been shown to be of benefit, particularly as maintenance therapy which is necessary for up to 1 or 2 years. Relapse can occur after many years: close, regular follow-up is essential [6].

Nephrotic Syndrome

Nephrotic syndrome is characterized by heavy proteinuria (greater than 3.5 g in a 24 h urine collection, protein to creatinine ratio greater than 3 g of protein per g of creatinine) in association with hypoalbuminemia, edema, and hyperlipidemia. In contrast to nephritic sediment, cellular casts and hematuria are uncommonly encountered in nephrotic syndrome.

Clinical and Laboratory Features

Heavy proteinuria is the hallmark of nephrotic syndrome, and nephrotic-range proteinuria is defined as greater than 3.5 g of proteinuria in a 24 h urine collection. Not all patients with nephrotic-range proteinuria have nephrotic syndrome, which is accompanied by edema, hypoalbuminemia, and hyperlipidemia. The typical presenting symptom of nephrotic syndrome is progressive edema. Edema generally starts in the lower extremities; periorbital edema, genital edema, ascites, pleural and pericardial effusions can be seen in advanced disease. Nephrotic syndrome should be suspected in patients with these findings in the absence of cirrhosis or congestive heart failure. The decrease in oncotic pressure from albumin loss, with a resultant movement of fluid from the intravascular space to the interstitial space, contributes to the edema. Recent studies have suggested the presence of increased renal sodium reabsorption in nephrotic syndrome, which may occur from both glomerular and tubulointerstitial factors. Severe tubulointerstitial inflammation in nephrotic syndrome has been theorized to increase vasoconstrictive agents (e.g., angiotensin II) while decreasing vasodilatory agents (e.g., nitric oxide) [7]. The 24 h urine collection remains the gold standard for quantifying proteinuria, although it has limitations in routine screening for proteinuria. Proteinuria evaluated by a urinalysis dipstick is a semiquantitative screening tool available to most physicians. In addition, the spot urine protein to creatinine ratio is easy to use in the clinic setting, and provides a quantitative value that accurately

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estimates the 24 h urine value. The value obtained from the spot urine (in mg/mg) will correlate to the protein excretion in grams per m^2 body surface area. Hypoalbuminemia is often less than 3 g/dL in patients with nephrotic syndrome, although the pathophysiology behind this remains incompletely understood. Most patients with nephrotic syndrome have hyperlipidemia, which may manifest as elevated total and low-density lipoprotein cholesterol, lipoprotein (a), and hypertriglyceridemia. The pathophysiological mechanism of hyperlipidemia likely occurs from increased hepatic synthesis, which is stimulated by decreased plasma oncotic pressure. In addition to these clinical symptoms of nephrotic syndrome, there are multiple additional potential complications encountered. Patients with marked proteinuria and hypoalbuminemia have a prothrombotic tendency, and experience increased risk of venous thromboembolism. Moreover, patients with membranous nephropathy as well as those with severe disease (albumin levels less than 2 mg/dL or proteinuria greater than 10 g in 24 h) appear to experience the highest risk of thromboembolic disease. In general, patients with nephrotic syndrome have a 1.7 relative risk increase in developing DVT compared to patients without it [8]. The cause of increased thrombosis is likely multifactorial, including increased fibrinogen levels, enhanced platelet aggregation, and loss of anticoagulants (such as antithrombin III) in the urine. Patients with nephrotic syndrome have increased susceptibility to infection, especially cellulitis and pneumococcal infection. Children and patients with frequent relapsing disease are at the highest risk. The pathophysiology is not completely understood, but urinary loss of IgG may play a role [9]. Finally, nephrotic syndrome can confer a negative protein balance, which can predispose patients to protein malnutrition. Decreased gastrointestinal absorption of protein from severe edema may play a role in this as well.

Etiology and Work Up

Heavy proteinuria and the nephrotic syndrome can occur from both primary kidney injury as well as secondary systemic diseases. In children, minimal change disease remains the most frequent cause of nephrotic syndrome. The two most commonly encountered primary or idiopathic causes of nephrotic syndrome are focal segmental glomerulosclerosis (FSGS) and membranous nephropathy, both of which can affect up to 30% of adults. In fact, in African-American adults, FSGS accounts for up to 50% of cases. Table 1 lists the most commonly encountered primary causes of nephrotic syndrome. Systemic diseases frequently lead to nephrotic syndrome in adults, with diabetes and systemic lupus erythematosus (SLE) the most common causes of secondary nephrotic syndrome (see list below). Accordingly, additional studies are often necessary to further investigate the possibility of a secondary etiology, which include but are not limited to: hemoglobin A1C complement, HIV screening test, hepatitis serologies (to investigate for hepatitis B and C), rapid plasma reagin (RPR) to evaluate for syphilis, serum and urine protein electrophoresis (to screen for multiple myeloma and amyloidosis), and antinuclear antibodies (for SLE evaluation). Although important to evaluate for hydronephrosis and cystic renal diseases, renal imaging will yield little in differentiating between the different causes of nephrotic syndrome, with the exception of enlarged kidney sizes in diabetes and infiltrative disease states. A kidney biopsy is often indicated to help

Table 1 Causes of primary nephrotic syndrome in adults

Idiopathic or primary nephrotic syndrome	Incidence (%)
Minimal change disease	10–15
Focal segmental glomerulosclerosis	20–30
Membranous nephropathy	25–40
Membranoproliferative glomerulonephritis	5
Other forms of glomerulonephritis	10–20

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diagnose the type of glomerular disease, identify subtype of disease, as well as to evaluate for activity and chronicity of illness. The results can help clinicians identify who will benefit from treatment. However, not all patients require a kidney biopsy, for example a patient with long standing diabetes with high clinical suspicion for diabetic nephropathy.

Causes of secondary nephrotic syndrome

- **Systemic Diseases**
  - Diabetes mellitus
  - Systemic lupus erythematous
  - Sarcoidosis
  - Rheumatoid arthritis
  - Amyloidosis (can be associated with AA or AL amyloid)
  - Vasculitis (cryoglobulinemia, Henoch-Schönlein purpura, etc.)
  - Celiac disease
  - Scleroderma
- **Infections**
  - Viral (hepatitis B, hepatitis C, HIV, mononucleosis)
  - Bacterial (streptococcal, syphilis, sub-acute bacterial endocarditis, shunt nephritis)
  - Parasitic (malaria, schistosomiasis)
- **Medications**
  - Nonsteroidal anti-inflammatory drugs
  - Gold, heavy metals
  - Lithium
  - Penicillamine
  - Captopril
  - Antibiotics (ampicillin, rifampin, etc.)
  - Bisphosphonates (pamidronate)
  - Anabolic steroids
  - Interferon
- **Neoplastic/malignancies**
  - Leukemia and lymphomas (typically minimal change disease)
  - Solid tumors (membranous)
- **Hereditary diseases**
  - Sickle cell disease
  - Fabry's disease
  - Alport's syndrome
  - Partial lipodystrophy
  - Nail-patella syndrome
  - Familial nephrotic syndrome
- **Others**
  - Pregnancy associated (pre-eclampsia)
  - Serum sickness
  - Obesity
  - Reflux nephropathy
  - Allergies (food, pollen, bee stings)

Minimal Change Disease

Minimal change disease (MCD) accounts for up to 90% of idiopathic nephrotic syndrome in children, and 10–15% in adults. MCD often presents suddenly, and can be associated with medications (nonsteroidal anti-inflammatory drugs) and hematological malignancies (leukemia and lymphomas). Treatment with high dose prednisone usually leads to remission. Because of the high rate of remission with steroids, kidney biopsies are generally not performed in children with new onset nephrotic syndrome until after a trial of prednisone. However, MCD can follow a course of remission and relapses; up to 50% of adults can relapse after 1 year. Alternative agents, including cyclophosphamide and cyclosporine, can be considered in patients with frequent relapses to decrease steroid exposure.

Focal Segmental Glomerulosclerosis

FSGS is the most common cause of nephrotic syndrome in African-Americans and accounts for up to 30% of lesions seen on kidney biopsies. FSGS can be idiopathic as well as seen secondary to HIV, obesity, and sickle cell disease, amongst others. Up to 40% of patients with FSGS have hypertension, hematuria, and decreased glomerular filtration rate upon presentation. Spontaneous remission is uncommon, and untreated patients with nephrotic range proteinuria often progress to ESKD within 5–10 years. Accordingly, patients with nephrotic range proteinuria are typically started on immunosuppressive agents, with prednisone being the most common initial agent. Response to therapy can preserve long-term renal function in FSGS, and glucocorticoids can lead to partial or complete remission of

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proteinuria in up to 60% of patients. Other immunosuppressive medications used in the treatment of FSGS include cyclosporine and mycophenolate mofetil, specifically in patients who relapse or to attenuate steroid exposure.

Membranous Nephropathy

Membranous nephropathy is the most common cause of idiopathic nephrotic syndrome in adults, occurring in up to 40% of cases in some biopsy series. Membranous nephropathy can be idiopathic or occur secondarily to systemic disease (SLE), medications, malignancies (solid tumors), and infections (hepatitis B and C). Recent studies have demonstrated an association between idiopathic membranous nephropathy with antibodies against phospholipase A2 receptors found on podocytes [10]. Membranous nephropathy is the most common type of nephrotic syndrome associated with prothrombotic events, including DVT and renal vein thrombosis. Spontaneous remission occurs in one third of patients, while one third have stable renal function longitudinally; the remaining third develop progressive renal failure. Because one third of patients do spontaneously remit, immunosuppressive treatment is generally reserved for patients who are at moderate to high risk for progressive renal failure. Factors associated with increased risk for progression include male gender, increased age, a decline in GFR over 3 months, and greater than 8 g of proteinuria. The most common initial immunosuppressive regimen includes 6 months of therapy with cyclophosphamide alternating with glucocorticoids on a monthly basis [11]. Alternatively, cyclosporine can be used as an induction agent, with increased rates of relapse once discontinued. More recently, rituximab can be used, primarily in patients with positive anti phospholipase A2 receptor status [12, 13].

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis is a rare type of nephrotic syndrome, accounting for approximately 5% of lesions seen on biopsy registries. There are two major types of MPGN. Type I is immune mediated and often associated with hepatitis C and/or cryoglobulins. Treatment usually centers on targeting the hepatitis virus. Type II MPGN, also called dense deposit disease, is rare and complement mediated.

Treatment

There are few placebo-controlled double-blind studies investigating the impact of immunosuppressive regimens on the different primary types of nephrotic syndrome, with commonly employed agents including glucocorticoids. Nonimmunosuppressive treatment modalities can be implemented for the nephrotic syndrome, regardless of the lesion seen on biopsy. It is important to limit sodium intake, often to less than 3 g/day. Furthermore, diuretics are frequently necessary to facilitate a negative sodium balance. Loop diuretics (furosemide and bumetanide) are first-line agents, and may be required to be administered via the intravenous route if there is a concern for intestinal edema in severe cases. In addition, patients may require a second thiazide-type diuretic (metolazone) in severe cases.

In addition to treating the edema associated with nephrotic syndrome, treatment should also target attenuating proteinuria. In addition to their antihypertensive effects, angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) reduce intraglomerular pressure; this in turn can reduce proteinuria [14]. The hyperlipidemia associated with nephrotic syndrome often resolves with treatment of the nephrotic syndrome. However, statin medications are often implemented to assist in controlling the lipid derangements.

Complications of nephrotic syndrome, specifically hypercoagulable disorders, are managed on an individual basis. Heparin, followed by warfarin, is used once a clot is detected. The use of prophylactic warfarin in patients at high risk remains controversial, but may carry greater benefit in patients with membranous nephropathy. Decision analysis tools such as GNTools have been developed to assist clinicians with risk-

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benefit analyses for anticoagulation in patients with membranous nephropathy [15].

Tubulointerstitial Diseases of the Kidney

Tubulointerstitial injury of the kidney may occur with any of the primary kidney disorders but also may be the principal manifestation of a diverse array of genetic, toxic, infectious, and metabolic diseases. Features usually include non-nephrotic range proteinuria, hematuria, pyuria, and a variety of tubular disorders such as renal tubular acidosis and nephrogenic diabetes insipidus. Cystic kidney diseases are the most common abnormality that the primary care physician first discovers. Cysts may be single or multiple and may be acquired, developmental, or genetic in origin. Cysts may be benign in nature but also may confer an increased risk of cancer. Table 3 details the different types of cystic kidney disease [16].

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is the most common inherited kidney disease and accounts for 10% of the ESKD population. Genetic mutations occur on either the short arm of chromosome 16 (PKD1) (85% of patients) or on chromosome 4 (PKD2) (15% of patients). Cysts usually arise from the distal tubules and may only affect a fraction of the tubules. These cysts enlarge and crowd out normal nephrons resulting in progressive kidney failure. There is great variability in this process which translates in a variable phenotype for a particular family. The diagnosis of ADPKD is usually confirmed with imaging studies and is age dependent. In patients with a family history and age < 40 years, more than 3 cysts in one or both kidneys establishes the diagnosis. In patients over 60 years, more than 4 cysts in both kidneys are required to establish the diagnosis. Progressive kidney disease is the norm for patients with ADPKD although the occurrence of ESKD is variable. Risk factors for a more rapid progression include family history, childhood onset, male gender, hypertension, urinary tract infection, kidney stones, black race, and sickle cell disease. Hypertension is very common and is sometimes used as a clinical marker for the disease especially when it occurs at a young age. Drugs that disrupt the renin–angiotensin axis are preferred as initial therapy although multiple drugs may be necessary as CKD progresses. Flank pain is the most common manifestation of the disorder and may be debilitating. Gross hematuria associated with cyst rupture, non-nephrotic range proteinuria, urinary tract infection, and kidney stones occur with increasing frequency. Several extrarenal manifestations of ADPKD often occur. Cysts can occur in other organs besides the kidney with the liver being most commonly involved. These cysts rarely produce organ failure but hemorrhage or infection can occur. Infections in any cyst may be difficult to treat as antibiotic penetration into the cyst fluid may be variable—recommended treatment includes antibiotics capable of penetrating the cyst wall such as trimethoprim-sulfamethoxazole, fluoroquinolones, erythromycin, tetracyclines, or metronidazole. Cyst drainage may be necessary to successfully eradicate the infection. The most devastating complication of ADPKD is rupture of an intracerebral aneurysm. Up to 4% of patients with ADPKD will have this complication, with a potential familial predilection. Patients with a family history of sudden noncardiac death or aneurysm should undergo screening. MRI angiography and preemptive repair may be indicated. Other complications of ADPKD include colonic diverticuli (80%) and cardiac valvular abnormalities (25%). Vasopressin V2 receptor antagonists (tolvaptan), mTor pathway inhibitors (sirolimus/everolimus), somatostatin analogs (octreotide, lantreotide), and statins (pravastatin) have all shown promise in slowing the progression of ADPKD. Large clinical trials are underway testing the benefits of these therapies that will alter the natural course of this devastating genetic disease [17]. Of the aforementioned therapies, tolvaptan has been most clearly demonstrated to slow progression of ADPKD, but careful monitoring of liver function is required [18].

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Table 3 Types of cystic kidney disease

Type of cystic kidney disease	Occurrence	Genetics	Radiographic appearance	Progression and complications	Risk of cancer
Simple cysts	Increase with age	Unknown	Solitary, multiple, round, smooth fluid filled	Usually none, no calcifications or hemorrhage	<1%
Complex cysts	Increase with age	Unknown	Solitary, multiple, septa, calcification, enhancement, irregular borders	Usually none, hemorrhage, infection	Increase with greater Bosniak category 5–90%
Acquired cystic disease ESRD	Increase with length of dialysis	Unknown	Similar to simple cysts	Similar to simple cysts unless malignant transformation	5–10%
ADPKD	>1:1,000 live births	PKD1 and PKD2 genes	Enlarged kidneys with numerous cysts	May progress to ESRD, bleeding, infection, kidney stones	Unknown
ARPKD	1:20,000 live births	PKHD1 gene	Enlarged kidneys with numerous, uniform cysts	Progressive loss of kidney function, hepatic fibrosis prominent feature	0
Medullary sponge kidney	Unknown	Unknown	Dilated collecting ducts	Usually none, kidney stones more common	0
Nephronophthisis	1:50,000 live births	Nine genes (ciliopathy)	Corticomedullary cysts with severe atrophy and scarring of cortex, small kidneys	Tubular dysfunction, sodium wasting, DI, RTA, ESRD by age 20	0

Chronic Interstitial Nephritis (CIN)

CIN includes a diverse group of diseases that culminate in prominent interstitial fibrosis and tubular atrophy. A similar disease, reflux nephropathy, affects the lower urinary track initially but invariably gives rise to chronic pyelonephritis and is usually discovered in childhood. Diseases in this group include urinary tract obstruction, prolonged ingestion of non-narcotic analgesics, urate nephropathy, hyperoxaluria, heavy metal poisoning with lead, cadmium or mercury, and infiltrative disorders such as lymphoma or sarcoidosis. Drugs that affect the interstitium include lithium, cisplatin, and calcineurin inhibitors such as cyclosporine. The clinical manifestations of CIN are often overlooked as they are often indolent. CKD occurs but progression is usually measured over a number of years. Renal tubular acidosis, nephrogenic diabetes insipidus, or Fanconi syndrome may be the predominant manifestation. Non-nephrotic range proteinuria with minimal albuminuria is often present. Renal sonography reveals shrunken, hyperechoic kidneys and a kidney biopsy is usually not helpful. There is no specific treatment for CIN except for treatment of the underlying disorder.

Acute Kidney Injury

Acute Kidney Injury (AKI) could be defined as abrupt (within 7 days) and sustained (over 24 h) decrease in glomerular filtration, urine output, or both. AKI is a common condition, which occurs in significant number of hospitalized patients and affects up to 50% of patients admitted to the ICU [19]. Importantly, community based cases comprise at least one third of all AKI cases [20]. Early stages of AKI might be difficult to recognize, as it does not have any specific symptoms. Detection might be particularly difficult in edematous

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Table 4 Stages of AKI

Stage	Assessment	
	Serum creatinine	Urine output
1	1.5–1.9× baseline or ≥ 0.3 mg/dl above baseline	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9× baseline	<0.5 ml/kg/h for 12 h
3	≥3.0 baseline, ≥ 4.0 mg/dl[a], or initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

[a]with an acute increase of at least 0.5 mg/dl

patients with fluid overload as they might have falsely lower levels of serum creatinine (SCr). AKI typically develops in the setting of another illness and is associated with high mortality, especially in patients requiring renal replacement therapy (RRT). Current guidelines define AKI as an elevation in SCr by ≥0.3 mg/dl within 48 h or urine output <0.5 ml/kg/h for 6 h. Stages of AKI are based on the severity of the impairment (Table 4).

The causes of AKI historically have been categorized into three groups: prerenal (caused by abnormal perfusion of the kidney), renal (due to intrinsic kidney damage), and postrenal (caused by obstruction of the urinary tract). AKI is a syndrome, it is important to determine the cause of it whenever possible. However, most of the AKI cases in the hospital are multifactorial in etiology.

Prerenal AKI accounts for 70% of AKI in the outpatient setting [21] and for 21% of AKI in the hospital [22]. Prerenal AKI is often reversible, but can lead to ischemic AKI if it is not timely addressed. Common causes include poor perfusion of the kidney due to hypovolemia, which could be caused by GI, renal or cutaneous losses or by blood loss. Decreased effective volume in patients with congestive heart failure or liver disease may cause prerenal AKI despite the total fluid overload and edematous state. ACE inhibitors and ARBs, nonsteroidal anti-inflammatory medications (NSAIDs) affect renal perfusion and glomerular filtration and can further promote prerenal AKI by impairing renal auto regulation in the setting of hypovolemia. Patients with CKD are especially susceptible to developing AKI [23]. Fractional Excretion of Sodium (FeNa) and Fractional Excretion of Urea (FeUr) are often used to differentiate between prerenal and renal causes of AKI. FeNa could be calculated using formula:

$$\text{FENa}\ (\%) = \left[\frac{(\text{NaU}(\text{mEq/L})/\text{Na}^{+}(\text{mEq/L}))/}{(\text{CrU}\ (\text{mg/dL})/\text{SCr}\ (\text{mg/dL}))}\right] \times 100$$

FeNa <1% is usually consistent with a prerenal cause of AKI, but it should be interpreted carefully. FeNa might be low in AKI patients with contrast nephropathy, rhabdomyolysis, and urinary tract obstruction [24] while diuretic use could be associated with FeNa >1%. In might be useful in evaluation of hepatorenal syndrome. Given limitations of FeNa FeUr is often used to distinguish prerenal and renal AKI. FeUr could be calculated using formula:

$$\text{FEUr}\ (\%) = \left[\frac{(\text{UrU}\ (\text{mg/dL})/\text{urea}\ (\text{mg/dL}))/}{(\text{CrU}\ (\text{mg/dL})/\text{SCr}\ (\text{mg/dL}))}\right] \times 100$$

A low FeUr (<35%) is usually indicative of prerenal AKI, but aging and sepsis may effect it. Urine fractional excretion indices might be helpful in AKI evaluation; a comprehensive clinical assessment should be used to determine volume status and guide therapy.

A blood urea nitrogen to creatinine ratio > 20 is often used to differentiate between prerenal and renal AKI. Recent data does not support its use as a marker for prerenal AKI [25, 26]. Evaluation of urine sediment could offer an additional information and urine microscopy should not be overlooked. Several biomarkers of AKI have been identified (IL-18, NGAL, LFABP and KIM-1, but their clinical applicability is limited [27].

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Intrinsic Renal AKI

Intrinsic renal causes could be further subdivided into tubular, glomerular, interstitial, or vascular based on the anatomical structure of the kidney. Acute tubular necrosis (ATN) is the most common cause of AKI in hospitalized patients. It is often a result of ischemia or exposure to nephrotoxins including antibiotics or radiocontrast medications. Muddy brown granular casts could be seen on urine microscopy. ATN often occurs with patients with predisposing conditions, it is usually reversible, but may require RRT. Glomerular causes include different types of glomerulonephritis like acute post infectious nephritis, lupus nephritis and RPGN among other types. In the presence of active urinary sediment showing proteinuria, hematuria or casts a prompt serological assessment is indicated. Rapid recognition and initiation of appropriate immunosuppressive agent is important to reduce the risk of complications and delay the progression of the disease. Interstitial causes included acute interstitial nephritis which could be caused by an allergic reaction to medications. It is often resolved with supportive treatment and withdrawal of the affecting agent. Eosinophiluria and white blood cell casts might be found on urine microscopy in some patients. Clinical symptoms may include maculopapular rash, fever, and arthralgias. Corticosteroids have a role in treatment of acute interstitial nephritis. Vascular causes of AKI comprise occlusion of the renal artery or disease of the abdominal aorta. Microvascular diseases include microangiopathic anemia due to thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, HELLP (*H*emolysis, *El*evated *L*iver enzymes, and *L*ow *p*latelets) and may require use of plasmopheresis for treatment. Atheroembolic disease as a cause of AKI should be suspected in a patient with recent arterial intervention or after vascular surgery.

Contrast Induced AKI (CI-AKI)

CI-AKI is one of the most common types of AKI found in a hospital setting. CI-AKI is often defined as an increase in serum creatinine of 0.5 mg/dL or 25% from baseline. It typically occurs within 48–72 h of exposure to iodinated contrast and often resolves over the following 1–3 weeks. It might be associated with the development of CKD in some cases. Patients with normal kidney function have minimal risk for CI-AKI. Patients with an estimated GFR < 60 mls/min/1.73 m^2, diabetes related CKD, congestive heart failure, vascular disease hadvanced age and hypotension are at increased risk. Critically ill patients are more vulnerable to CI-AKI. Medications altering renal perfusions like diuretics, ACEi, ARBs and NSAIDs should be held in the morning of procedure if possible and not restarted back until 48 h after contrast administration if creatinine is stable. Unenhanced scanning, low or iso-osmolar iodinated contrast medium should be considered for those who are at risk for developing CI-AKI. Intravenous volume expansion with either 0.9% sodium chloride or isotonic sodium bicarbonate is recommended in patients identified as at risk of CI-AKI [28]. Common regimen includes infusion at a rate of 1 ml/kg given for 12 h before and after the contrast. Shorter regimen at a rate of 3 ml/kg per h for 1 h before the contrast administration and 1 ml/kg per h for 6 h after may be used if needed. *N*-Acetylcysteine is commonly used for CI-AKI prevention due to low cost and lack of the harm data, however recent data does not support its benefits [29].

Postrenal AKI

Postrenal AKI accounts for up to 10% of the hospital and 17% of the community AKI cases respectively and results from an obstruction of urine flow at different levels. Both urinary tracts need to be obstructed for AKI to develop unless the patient has a single functioning kidney. Obstruction could be mechanical (prostate hypertrophy, prostate and cervical cancer, retroperitoneal fibrosis) or functional (neurogenic bladder). Papillary necrosis can cause intrarenal obstruction and lead to AKI. Relieving obstruction is the ultimate treatment and should be done promptly to improve the chance of recovery.

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AKI Risk Factors

A number of chronic diseases including diabetes mellitus and cardiovascular disease are associated with AKI development. CKD and proteinuria [30] are proven to be risk factors for AKI as well as older age, female gender, volume contraction, solitary kidney, septic shock, obesity, use of the nephrotoxic drugs [31] (see list below), blood product transfusion, and underlying chronic heart, lung, and liver disease [32].

Drugs that contribute to AKI

- Radiocontrast agents
- Aminoglycosides
- Amphotericin
- Nonsteroidal anti-inflammatory drugs
- β-lactam antibiotics (specifically contribute to interstitial nephropathy)
- Sulphonamides
- Aciclovir
- Methotrexate
- Cisplatin
- Ciclosporin
- Tacrolimus
- Angiotensin-converting-enzyme inhibitors
- Angiotensin-receptor blockers

Diagnostic Evaluation

Careful interpretation of clinical history, physical exam findings, and laboratory values is very important (Fig. 1). SCr is affected by a number of different factors including nutrition, muscle mass, steroid use, presence of gastrointestinal bleeding, age, sex, and muscle injury. SCr may not change until glomerular filtration decreases by 50%. Measurement of creatine kinase might be helpful in suspected cases of rhabdomyolysis, while the measurement of inflammatory markers and assays that detect specific antibodies (anti-GBM, ANCA anti-DNA) is helpful to diagnose vasculitis or glomerulonephritis. Haptoglobin, lactic dehydrogenase, bilirubin, and free hemoglobin should be measured if the diagnosis of thrombotic thrombocytopenic purpura is considered. Peripheral smear with the finding of schistocytes may support the diagnosis of microangiopathic hemolysis. Finding monoclonal proteins in serum and/or urine might provide diagnostic clues and point towards multiple myeloma and amyloidosis. In some cases, when clinical history, diagnosis and imaging tests are not sufficient, renal biopsy might be needed to establish the diagnosis. Renal ultrasound should be considered in most patients, specifically in older men. Finding of >50–100 ml on the bladder scan in a patient with AKI should raise suspicion for postrenal causes.

Prevention and Treatment of AKI

Prevention of AKI relies on an earlier recognition of its potential causes, avoidance of possible renal insults whenever possible, and treatment of suspected AKI triggers to minimize damage. Most of the patients with AKI will require comanagement between primary care physicians, hospitalists, nephrologists, and other subspecialists depending on the underlying disease process. Treatment of AKI should include thorough assessment and is mainly supportive. It includes monitoring of volume status, SCr, urine output and management and treatment of underlying cause. Renal doses of medications should be used and nephrotoxic medications should be avoided. Drug monitoring should be used, whenever possible, to guide the therapy, specifically for vancomycin, aminoglycosides, and other medications. When fluid resuscitation is required, isotonic crystalloid solutions are preferred. Small boluses (500 ml over 30 min) can given followed by an assessment of cardiac output. Urine output should be carefully charted and fluids should be discontinued if oliguria persists. In patients with fluid overload and those who present with acute decompensated heart failure and cardiorenal syndrome, loop diuretics either as continuous infusion or intermediate dose boluses could be used with close monitoring of serum electrolytes [33]. Patients who present with severe hyperkalemia or have EKG changes should be treated with intravenous calcium gluconate (10 mL of 10% solution infused over 5 min) to stabilize the cardiac cell membrane. IV insulin (5–10 units with 12.5 or 25 g of dextrose) with or without a β_2-Adrenergic agonist

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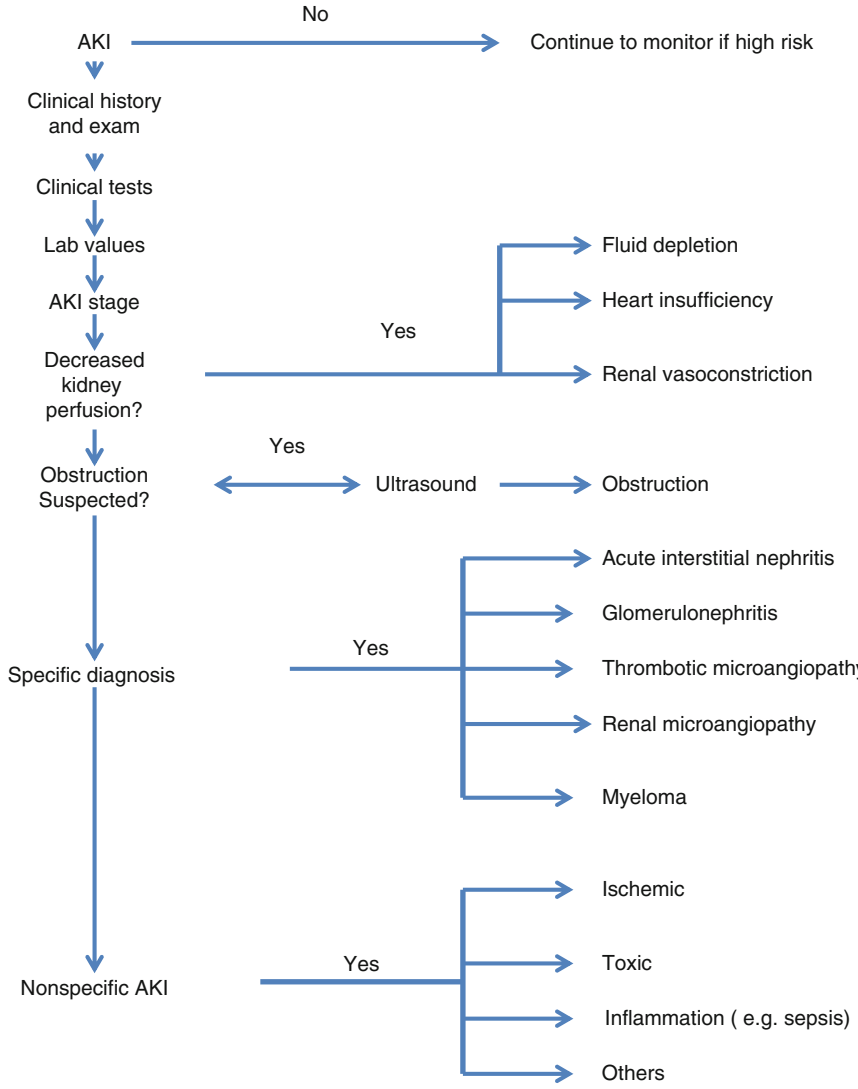


Fig. 1 Evaluation of AKI

could be used to lower potassium by causing intracellular shift. When administered together they work better than either medication alone; rebound occurs in about 1–2 h. Delivery of caloric intake at 20–30 kcal/kg/day in patients with any stage of AKI is recommended [28], enteral nutrition is preferred. After nephrology consult is obtained, consideration might be given to a renal biopsy and disease specific treatment (steroids, plasmapheresis, immunosuppressive therapy) might be initiated. For patients who do not improve with conservative management or exhibit uremic complications like difficult to control hyperkalemia, metabolic acidosis or volume overload, RRT might be required.

Follow Up Care

AKI is an important risk factor for CKD even among patients who recovered completely from this condition. Severity and number of AKI episodes are risks for development of CKD [34]. Patients with history of AKI should be reevaluated in 3 months for AKI resolution, new onset, or worsening of CKD [28].

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CKD

CKD is a worldwide problem and is associated with increased mortality, morbidity, and health care costs. Disease affects an estimated 15% or approximately 37 million adults in the United States and it is the 9th leading cause of death. One out of three patients with diabetes and one out of five patients with hypertension might have CKD [35]. CKD is more common in patients aged 65 years or older and seen more frequently in women. Patients with CKD are at significantly increased risk for cardiovascular disease and stroke [36, 37]. Incidence and prevalence of CKD has continued to rise which might be explained by the increasing prevalence of diabetes mellitus and hypertension, the leading risk factors for CKD. The incidence of CKD stage 5 requiring dialysis or transplantation is the US is the highest in the world, but might be on the decline due to improvements in the prevention and treatment of CKD. About 1% of CKD patients are treated with dialysis and/or kidney transplantation, primary care physicians manage most of the nondialysis CKD patients.

CKD Definition and Detection

CKD is defined as abnormality of kidney structure or function with or without an accompanying reduction in Glomerular Filtration Rate (GFR), present for over 3 months, with implications for health.

Markers of kidney damage include presence of albuminuria, urine sediment abnormalities, electrolyte abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities found on imaging and history of kidney transplant. Patients with CKD may have decreased estimated GFR (eGFR). eGFR of less than 60 mL per minute per 1.73 m^2 for at least 3 months is indicative of CKD. CKD is classified into five stages on the basis of eGFR. Normal GFR in young adults is around 125 mL/min per 1.73 m^2; eGFR <15 mL/min per 1.73 m^2 is defined as kidney failure. Presence of albuminuria even with normal eGFR signifies CKD. Patients with eGFR <45 ml/min per 1.73 m^2 experience faster disease progression [38]. Proteinuria affects CKD evolution and influences mortality [39]. Table 6 outlines prognosis of CKD by eGFR and albuminuria categories [39].

It is now recognized that CKD and AKI are closely connected: AKI can lead to CKD, if duration of the abnormal GFR is unknown, the possibility of AKI should be considered and a timely appropriate evaluation should performed to identify reversible causes. CKD is a risk factor for developing AKI, patients with CKD are 10 times more likely to develop AKI than those without CKD [40]. Patients who are older, have diabetes, hypertension, obese, and those with cardiovascular disease are at risk for CKD. CKD is often asymptomatic until advanced stages. It makes screening and early identification with two simple tests: eGFR and urine albumin to creatinine ratio very important. When symptoms are present, they include fatigue, hypertension, edema, shortness of breath, leg cramps, poor appetite, and abnormal urination pattern. Annual CKD screening for patients at risk (patients with diabetes, hypertension, cardiovascular disease) is recommended by several professional organizations [41, 42]. The

Table 6 Prognosis of CKD by eGFR and albuminuria categories

Persistent albuminuria categories				
Stage	GFR ml/min/1.73 m^2	<30 mg/g	30–300 mg/g	>300 mg/g
1	≥90 normal or high	Low risk	Moderate risk	High risk
2	60–89 mildly decreased	Low risk	Moderate risk	High risk
3A	45–59 mildly to moderately decreased	Moderate risk	High risk	Very high risk
3B	30–44 moderately to severely decreased	High risk	Very high risk	Very high risk
4	15–29 severely decreased	Very high risk	Very high risk	Very high risk
5	<15 kidney failure	Very high risk	Very high risk	Very high risk

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evidence to support CKD screening in asymptomatic adults without risk factors or family history of CKD is lacking.

Etiology

Although the most common causes of CKD are diabetes and hypertension, which account for over two thirds of all CKD cases, CKD can be caused by many other conditions (Table 7). Diabetic kidney disease develops in 20–40% of diabetic patients and characterized by slowly progressing albuminuria associated with eGFR decline, elevated blood pressure and increased cardiovascular morbidity and mortality. Untreated albuminuria progresses from microalbuminuria (30–300 mg/g creatinine, albuminuria grade A2) to clinical albuminuria (> 300 mg/g creatinine, albuminuria grade A3) over 5–15 years and can reach "nephrotic range." "Nephrotic range "proteinuria is diagnosed when albumin to creatinine ratio is over 2,200 mg/g or protein to creatinine ration is over 3,000 m/g, Nephrotic range proteinuria in the presence of hypoalbuminemia and edema defines nephrotic syndrome. Hypertensive kidney disease might be associated with albuminuria that develops after eGFR decline. Black patients are at much higher risk for developing hypertension induced end stage kidney disease. Urinalysis might be helpful as it can provide diagnostic clues to detection of glomerulonephritis, tubulointerstitial disease, vasculitis, hereditary nephritis, and lupus nephritis.

A thorough investigation is important in assessing CKD and includes determining etiology and type of CKD whenever possible and evaluating for comorbidities. Proteinuria refers to an increased excretion of any urinary proteins, including albumin and other serum proteins (tubular proteins). A normal urinary protein-to-creatinine ratio is less than 200 mg per g; proteinuria is predictor of total mortality and CKD progression and can help determine the type of CKD. Albuminuria is an abnormal excretion of albumin when albumin-to-creatinine ratio exceeds 30 mg per g. Albuminuria on a random nontimed urine should be confirmed with subsequent early morning urine sample. If significant, nonalbumin proteinuria is suspected, assays for detection of Bence Jones proteins should be used. Albuminuria and eGFR should be assessed annually for patients with CKD [39] and small variations in eGFR are common and might not indicate progression. Rapid progression is defined as drop of 5 ml/min/1.73 m^2 per year. At the time of CKD diagnosis all patients should be assessed to identify the risk factors for progression that include: cause of CKD, stage of CKD using eGFR and albuminuria (lower GFR levels and higher degree of albuminuria are associated with CKD progression). Other factors contributing to CKD progression include age, race/ethnicity, elevated blood pressure, hyperglycemia, dyslipidemia, smoking, and exposure to nephrotoxic drugs.

Table 7 Etiology of CKD

Diabetic kidney disease	Diabetes Mellitus Type 2
	Diabetes Mellitus Type 1
Nondiabetic kidney disease	
Vascular diseases	Hypertension, ischemic renal disease
Glomerular diseases	*Primary*: Lupus nephritis, vasculitis, membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, immunoglobulin A nephropathy
	Secondary: Infections (e.g., hepatitis B and C, human immunodeficiency virus–associated bacterial endocarditis), amyloidosis, heroin use, malignancy (e.g., leukemia, Hodgkin lymphoma, carcinoma)
Cystic diseases	Polycystic kidney disease
Tubulointerstitial disease	Urinary tract infections, nephrolithiasis, obstruction, sarcoidosis, multiple myeloma, drug toxicity (e.g., proton pump inhibitors, lithium, nonsteroidal anti-inflammatory drugs)

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Treatment

The goals of CKD treatment is to slow progression of CKD, reduce compilations of decreased eGFR, reduce risk of cardiovascular disease, and improve survival and quality of life. Death is more likely than progression to dialysis in any stage of CKD [42]; an assessment of cardiovascular risk factors including smoking status, and dyslipidemia is very important. Salt intake should be reduced to less than 2 g of sodium a day (less than 5 g of sodium chloride). Patients with CKD should be encouraged to participate in physical activity 30 min, five times a week. Target for Hg A1C in diabetic patients is about 7% or less to prevent or slow down the progression of kidney disease. For patients with comorbidities, reduced life expectancy, and those who are at risk for hypoglycemia HgA1c goals should be loose and increased to closer to 8% [34]. Best HgA1c attainable should be achieved whenever possible. Metformin may be continued in people with diabetic kidney disease and eGFR $\geq$45 ml/min/1.73 m^2. Its use should be reviewed in patients with GFR 30–45 ml/min/1.73 m^2 and it should be stopped when GFR is 30 ml/min/1.73 m^2 or less [39]. The sodium glucose transporter-2 (SGLT2) inhibitors, a new class of diabetic medications, might offer renal protection, slow down eGFR decline and reduce the degree of albuminuria [43].

Therapeutic strategies that have been shown to prevent cardiovascular events in patients with CKD include BP control, statins, and use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. The optimal blood pressure goal is the area of controversy. JNC 8 recommends blood pressure goal of less than 140/90 for patients with diabetes and nondiabetic CKD [44]. The American College of Cardiology/American Heart Association 2017 Hypertension Guidelines set a BP goal of $<$130/80 mm Hg for patients with CKD [45].

Use of ACE inhibitors and ARBs in CKD patients is associated with delaying CKD progression including in patients with advanced disease stages and, importantly, offers a greater survival. Medications could be stopped temporarily in the setting of AKI and should be restarted when creatinine stabilizes. In patients with cardiovascular disease and CKD, levels of cardiac biomarkers like BNP and troponin could be used for prognostication and cardiovascular risk stratification, but diagnostic utility is unclear. Patients with eGFR of less than 60 mL per minute per 1.73 m^2 require further evaluation to assess for CKD complications. Evaluation for anemia is recommended in women with hemoglobin levels less than 12 g per dL (120 g per L) and in men with levels less than 13.5 g per dL (135 g per L), in addition to nutritional assessment and evaluation for bone disease. Hemoglobin goals should not exceed 11 g per dL (110 g per L) in patients receiving erythropoiesis-stimulating agents due to the risk of major cardiovascular events. Referral to a nephrologist is recommended for patients with CKD stage 4 and for patients who meet other criteria for referral including albuminuria (ACR ratio $>$ 300 mg/g), nephrotic range proteinuria, resistant hypertension, hyperkalemia, hereditary kidney disease and hematuria not secondary to urologic conditions. Doses of medications should be adjusted; decreased eGFR affects pharmacokinetics and pharmacodynamics of many medications, increasing the risk of toxicity. Multispecialty team including nephrologist should manage patients with advanced stages of CKD. Renal replacement therapy when eGFR falls below 10 ml/min/1.73 m^2 might need to be initiated to manage symptoms of kidney failure (serositis), acid-based and electrolyte abnormalities, control volume status, and blood pressure. Preemptive renal transplantation should be considered for patients with eGFR less than 20 ml/min/1.73 m^2 with evidence of progressive and irreversible decline over the preceding 6–12 months. Advanced planning should be offered to all patients with CKD and end of life care discussion should be cared on with those choosing conservative care for CKD.

Renal Cell Carcinoma

Renal-cell carcinomas account for approximately 3% of adult malignancies and for 90–95% of kidney cancers and originate from renal

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epithelium. Genetic and environmental factors influence disease development. Established risk factors include active and passive smoking, hypertension and obesity. Acquired renal cystic disease, ESKD, duration of dialysis and tuberous sclerosis are all associated with increased risk for developing renal cell carcinoma. Males have higher predominance than females and disease peaks in sixties and seventies. Clear cell carcinomas account for 70–85% of renal cell carcinomas followed by papillary type that accounts for 7–15%: approximately 2–3% of the cases are genetic. Von Hippel-Lindau syndrome (occurring 1 in 36,000 births) is an autosomal dominant cancer disorder and is associated with retinal angiomas, hemangioblastomas of the central nervous system and clear cell type renal cell carcinomas. The gene responsible for that syndrome is located on chromosome 3 (3p25–26) [46]. Patients with this syndrome develop multifocal and often bilateral renal tumors earlier in life; they require monitoring of lesions size. Only about 10% of all patients present with classic triad of symptoms: flank pain, palpable abdominal mass and hematuria and over 50% of the tumors are found on the unrelated imaging studies [47] Some patients might present with nonspecific symptoms like fatigue, weight loss, anemia, and micro or gross hematuria. Hematuria should always be promptly evaluated by computed tomography (CT) to rule out a renal mass and patients older than 35 or with risk factors may require cystoscopy to rule our bladder carcinoma as well. The paraneoplastic syndromes seen in patients with renal cell carcinoma include polycythemia from abnormal erythropoietin production, unexplained fever, hypercalcemia, and Stauffer syndrome: cholestatic jaundice and organomegaly in the absence of liver metastasis. For smaller tumors detected early consideration can be given to nephron sparing surgery, thermal ablation or surveillance as treatment options. Nephrectomy (partial or total) is indicated for larger and central tumors. Radio frequency or cryoablative treatments are alternative approaches, especially in patients with small cortical tumors, hereditary RCC, and multiple bilateral tumors. Prognosis depends on the stage and histological subtype. Approach and type of the surgery depends on the size, location, TNM classification, and other anatomical considerations. About one -third of the patients who undergo surgical treatment for localized disease will have recurrence. Median survival varies from 8.8 to 27 months based on the number of risk factors present.

Transitional Cell Carcinoma

Renal transitional cell carcinoma or renal urothelial carcinoma is a rear type of kidney cancer arising from the transitional (urothelial) cell lining of the urinary tract and accounts for approximately 7% of all kidney tumors. It is the most common cancer of the renal pelvis. Risks factors include smoking, carcinogens exposure, and analgesic use. Most of the patients present with microscopic or macroscopic hematuria. Patients with upper urinary tract urothelial cancer are at risk for the development of bladder urothelial cancer. Men are affected more frequently. Over 90% of patients with superficial and confined disease to the renal pelvis or ureter could be cured. The cure rate drops to 10–15% for those with deeply invasive tumors that are still limited to the renal pelvis or ureter. Patients with cancer spread through the uroepithelial wall or with distant metastases have poor prognosis. The main prognostic factor is the degree of the invasion into or through the uroepithelial wall. Tumor grade is another prognostic factor, stage and grade correlate in over 80% of cases. Surgical treatment (laparoscopic or open) varies from conservative to total excision of the ureter with a bladder cuff, renal pelvis, and kidney in an attempt to offer the best chance for cure. Chemotherapy with cisplatin-based taxanes and/or gemcitabine agents could be used as an adjuvant to a surgical treatment, for those who are not candidates due to advanced disease or poor general condition or for patients with metastatic disease [48]. The role of radiation treatment is not well stated, but might be beneficial to patients with stages T3/T4 cancer [48].

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Bladder Cancer

Bladder cancer is the fourth most common cancer in men. The chance men will acquire it during their life is about 1 in 26; for women, the chance is about 1 in 90 [48]. Over 90% of the bladder cancer is transitional (urothelial) cell carcinomas. Squamous cell carcinoma accounts for about 5% of bladder cancers in US and less than 2% are adenocarcinomas. On initial presentation 55–60% of patients have low grade non-invasive disease that can be treated conservatively and 4% present with distant metastasis. The incidence of bladder cancer increases with age peaking between 50 and 70 years, average age at the time of the diagnosis is 73 years of age. Risk factors for bladder cancer include smoking, environmental and chemical exposures, chronic irritation and infections, and genetic and molecular abnormalities. Patients treated with long-term cyclophosphamide are also at risk. The main symptom is gross painless hematuria; other symptoms like increased frequency, urgency and feeling irritation with voiding should raise a concern for bladder cancer. Evaluation includes urine cytology, cystoscopy, and imaging studies [49]. Several urine tumor markers are commercially available, they have high false-positive and false-negative rates and their role in detection and surveillance of the bladder cancer is controversial [50]. The diagnosis and stage is established by transurethral resection with several options available for urinary diversion. Because of the high recurrence rate regular surveillance is critical in management of bladder cancer. After transurethral resection of the tumor, patients need cystoscopy and voided urine cytology every 3 months for 2 years, then 6 months for 2 years, and then once yearly, indefinitely [49]. Imaging to the upper urinary tract every 12–24 months is also recommended to monitor for cancer occurrence. Intravesicular treatment with the BCG and interferon alfa, mitomycin, doxorubicin, thiotepa or gemcitabine could be used to reduce the recurrence.

Wilms' Tumor

Wilms' tumor or nephroblastoma amounts for about 7% of all cancers in children, and it is the most common renal neoplasm in pediatric patients. Boys and girls are evenly affected by this disease. 10% of the children with this disease have other congenital abnormalities. Wilms'-tumor is usually unilateral, but 5% of the patients develop lesions in the second kidney or have bilateral disease. The mean age for the genetic type is 2 years of age and for sporadic cases is 3 years of age. Some patients may present with abdominal pain and hematuria, but most commonly, patients present with abdominal mass found by caregivers or pediatricians. About one fourth of the patients have hypertension due to an excessive renal secretion of renin secondary to renal ischemia produced by the mechanical effect of the tumor. CT or MRI of the abdomen is used for diagnosis and staging. Wilms' tumor metastasizes to the abdominal lymph nodes, lungs, and liver. Wilms' tumor has a favorable prognosis. It is a curable disease and nearly 90% of the patients with Wilms' tumor have over 5 years survival rate. Prognosis depends on a number of factors including tumor size, stage of the disease, histopathologic type, and on presence of biological markers of poor prognosis including mutations of *WT1*, 1q gain, alterations at 17p, LOH at 4p and 14q, *MYCN* amplification, and LOH at 11q. Overall, patients with anaplastic Wilms tumor have a worse prognosis. All patients with this tumor should be considered for entry into clinical trials.

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Benign Prostate Conditions

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Lower Urinary Tract Symptoms

Lower urinary tract symptoms (LUTS) encompasses a range of bladder storage and voiding symptoms that can include urinary frequency, urgency, nocturia, weak stream, hesitancy, intermittency (starting and stopping), and a sense of incomplete emptying. Dysuria, pain, or discomfort in the bladder and genital areas, hematuria, and urinary incontinence are other symptoms that can be associated with the infectious, inflammatory, and neoplastic prostate conditions that cause LUTS. Many men experience these types of urinary symptoms. A study of 30,000 patients over age 40 in the USA, UK, and Sweden showed that 72.3% of the men had LUTS at least "sometimes," and 47.9% had LUTS at least "often" [1].

Three of the most important potential causes of LUTS in men are prostatic hyperplasia, prostatitis, and prostate cancer, but other causes also need to be considered. For example, medical problems that increase urine volume may present with LUTS, such as poorly controlled diabetes mellitus, heart failure, or use of diuretic medicines. Some medications, particularly those with anticholinergic effects, can lead to urinary retention, which may cause or exacerbate LUTS. Infectious causes of LUTS include urinary tract infections, sexually transmitted infections, and other problems such as epididymitis. Kidney and bladder stones can cause LUTS, as can other serious problems that may present with microscopic or gross hematuria, such as bladder cancer and kidney cancer. Men with pelvic floor muscle dysfunction may have LUTS from overactive bladder or they may experience urinary incontinence.

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International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS score							

Score 1–7: *Mild* 8–19: *Moderate* 20–35: *Severe*

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Fig. 1 International Prostate Symptom Score (IPSS). Found at: https://musculoskeletalkey.com/benign-prostatic-hyperplasia/. (From Kellerman R, Rakel R. Conn's current therapy 2020, Saunders 2020. International Prostate Symptom Score (IPSS) questionnaire, available from the urological Sciences Research Foundation at www.usrf.org/questionnaires/UA_SymptomScore.html)

The severity of LUTS can be quantified using a self-administered patient questionnaire called the International Prostate Symptom Score (IPSS) (Fig. 1). To complete it, the patient ranks each of 7 symptoms on a 1–5 scale [2], with an additional question to assess the impact on quality of life. This questionnaire has been well studied in men. Scores from 0 to 7 indicate mild symptoms, 8 to 19 indicate moderate symptoms, and 20 to 35 indicate severe symptoms. Printable versions of the IPSS questionnaire can readily be found online. The IPSS does not directly assess dysuria, pain,

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hematuria, or incontinence, so clinicians will want to also ask about these symptoms.

The initial approach to a male patient with LUTS is to obtain a thorough history and quantify the symptoms and their impact using the IPSS. Ask about dysuria, fever, chills, penile discharge, suprapubic or genital pain, gross hematuria, urinary incontinence, and any risk factors for sexually transmitted infections. Assess tobacco use history, because smoking increases the risk of bladder and kidney cancers. Ask about other medical problems, such as diabetes or kidney stones. Review the patient's current medications and consider if they might affect urination. Ask if there is any family history of urinary problems, such as kidney stones or prostate cancer.

The approach to the physical exam for patients with LUTS is guided by the history. Palpate the abdomen for masses or tenderness, and percuss the kidneys to check for costovertebral angle tenderness that may indicate pyelonephritis or kidney stones. Palpate the scrotum to assess for epididymitis, orchitis, and testicular masses. Examine the penis for balanitis, skin lesions such as herpes simplex, and anatomic abnormalities like hypospadias that can increase risk of urinary tract infection. Look for urethral discharge that might indicate urethritis. Digital rectal exam of the prostate is helpful to evaluate for evidence of prostatic hyperplasia, prostatitis, and prostate cancer.

The initial laboratory and diagnostic evaluation for a male with LUTS is guided by the history and physical examination. If a sexually transmitted infection is possible, the first step is to collect an initial first-catch urine sample (without cleansing the tip of the penis) to send for gonorrhea and Chlamydia testing. For all patients with LUTS, also collect a mid-stream clean-catch urine sample and do a urinalysis (UA). If the UA appears to show hematuria, also do a urine microscopic evaluation to confirm this (at least three to five RBC/HPF is considered positive). When a urinary tract infection is suspected, send the clean-catch urine sample for culture.

After the patient has urinated, measure the bladder post-void residual volume (PVR) with ultrasound to evaluate for urinary retention. Ultrasound measurement of PVR is more reliable than physical examination and less invasive than catheterization, and it can easily be done using a dedicated portable bladder-scan machine. With proper documentation, this is a billable procedure under CPT 51798. Normal PVR volumes vary, but about 60% of men will completely empty their bladders (PVR $\leq$10 mL) [3]. A PVR over 180 mL has been associated with an increased risk of bacteriuria. Elevated PVR volume can be due to bladder outlet obstruction, bladder detrusor dysfunction, or both. Some specialized tests that are typically done by urologists and can be useful in diagnosing patients with LUTS include measuring urine flow rate and testing bladder function with urodynamic studies.

Blood tests can be useful for some men with LUTS. Prostate specific antigen (PSA) results can help determine if the patient needs further evaluation for prostate cancer. Check PSA for symptomatic men age $\geq$50 years, or men age $\geq$40 years who are at increased risk of prostate cancer due to their family history or African-American ethnicity. Also check PSA for all men with a palpable prostate nodule. Be aware that the PSA will almost always be elevated in a man with an acute febrile urinary tract infection, and it will typically remain elevated for several months after the infection resolves, so the result must be interpreted in clinical context [4]. It is also reasonable to evaluate men with LUTS for diabetes, using A1c or fasting glucose, and to assess their renal function with a metabolic panel.

Management of LUTS depends on the cause. Approaches to prostatic hyperplasia and prostatitis are detailed below, and prostate cancer is addressed in a separate chapter. The initial evaluation and treatment of most causes of LUTS is generally done by the patient's family physician. Consult a urologist when the diagnosis is unclear, the patient is not improving, or if a procedure such as cystoscopy or prostate biopsy may be indicated.

Prostatic Hyperplasia

The prostate gets bigger as a man ages. This growth process is called benign prostatic hyperplasia (BPH). ("Hyperplasia" means that the number of

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prostate cells is increasing, as opposed to the older term "hypertrophy" which implied that the cells were just getting bigger.) Autopsy studies show that BPH is present in about 20% of men in their 40s, 40% of men in their 50s, 70% of men in their 60s, and 80–90% of men age 70 or older [5].

Although a prostate that is over 30 mL in volume is often considered to be "enlarged," prostate size does not correlate well with symptoms [6]. When prostatic enlargement is associated with symptoms, the most common reason is that the prostate has caused some degree of bladder outlet obstruction. Hyperplasia of the transitional zone of the prostate can press on the urethra at the bladder outlet, and the resulting obstruction can cause a slow urinary stream, hesitancy, intermittency, and incomplete emptying. Men with bladder outlet obstruction are at increased risk of acute and chronic urinary retention, as well as urinary tract infections and bladder stones. If ongoing bladder outlet obstruction causes the bladder smooth muscle to become overactive, symptoms can include urinary urgency, frequency, and nocturia. However, men with slowly progressive obstructive disease may be asymptomatic. Longstanding bladder outlet obstruction can lead to bladder distention, urinary incontinence, hydronephrosis, hypertension, and chronic kidney disease.

Additionally, BPH can cause gross or microscopic hematuria, but other causes of blood in the urine need to be ruled out. An evaluation of an adult with hematuria should include imaging of the kidneys and upper urinary tracts, usually using CT urogram (performed with and without contrast), to assess for both renal cell carcinoma and kidney stones, plus a cystoscopy to look for bladder cancer or bladder stones.

The causes of BPH, which occurs mostly after age 40, are not fully understood, but exposure to androgens is a major factor. Testosterone stimulates prostate growth, and testosterone is itself converted by the enzyme 5-alpha-reductase into dihydrotestosterone, which is another androgen five to ten times more active than testosterone in stimulating prostate growth. Other factors also appear to stimulate BPH, such as the inflammation associated with problems such as obesity, diabetes, and metabolic syndrome.

The approach to a patient with suspected BPH starts with history gathering and administration of the IPSS questionnaire (Fig. 1). The severity of symptoms and their effects on quality of life are key factors when choosing treatment options. Ask about the time frame over which symptoms occurred. BPH symptoms tend to progress gradually over years. Key elements of the physical exam include the abdominal exam, genital exam, and a digital rectal exam of the prostate. An enlarged prostate that is symmetric and smooth supports a diagnosis of BPH. Urinalysis and measurement of bladder post-void residual volume are helpful tests. Check PSA whenever prostatic hyperplasia is suspected. Although BPH is not a risk factor for prostate cancer, BPH and prostate cancer occur in the same patient population. When the PSA is elevated above the normal range for the patient's age, urology consultation is indicated, and prostate biopsy may be needed.

Lifestyle changes are a reasonable initial approach to managing BPH, and they may be sufficient for some men with mild BPH symptoms. Recommend avoidance of bladder irritants such as caffeine, weight loss as needed to maintain a body mass index (BMI) below 25 kg/m^2, and regular exercise.

Consider prescribing medicine to treat BPH when symptoms have become bothersome, when urinary retention is present, or if the patient has had other complications of BPH, such as a urinary tract infection. Initial medication treatment is usually with an alpha blocker, such as tamsulosin (Flomax) 0.4 mg daily, alfuzosin (Uroxatral) 10 mg daily, or silodosin (Rapaflo) 8 mg daily. Older alpha blockers such as terazosin (Hytrin) or doxazosin (Cardura) can be used, but they are more likely to cause orthostatic hypotension, so the dose should be titrated up slowly. Symptom relief is often noted within the first few days of treatment with an alpha blocker. The most common side effect of alpha blockers is hypotension. Some men may note retrograde ejaculations, also called dry ejaculations.

A second category of medicines useful for treating moderate to severe symptomatic BPH in men with prostates larger than 40 mL size is the 5-alpha reductase inhibitors, which inhibit the

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conversion of testosterone to dihydrotestosterone. Typical dosing for BPH is finasteride (Proscar) 5 mg daily or dutasteride (Avodart) 0.5 mg daily. These medicines work slowly to decrease prostate size, with the resulting effect of also artificially lowering PSA by about 50% after 6–12 months of treatment [7]. This decrease in PSA can obscure PSA changes due to prostate cancer, so be sure to obtain a baseline PSA before prescribing a 5-alpha reductase inhibitor, and continue to monitor PSA at least annually for patients taking these medicines. Adverse effects in some men may include decreased libido or erectile dysfunction. Gynecomastia also can occur.

The US Food and Drug Administration (FDA) has also approved the use of tadalafil (Cialis), a phosphodiesterase type 5 inhibitor, for treating symptomatic BPH. For men with BPH, tadalafil dosing is 5 mg daily. Tadalafil is a long-acting medication that is also used for erectile dysfunction. When prescribed for erectile dysfunction, typical tadalafil dosing is 10–20 mg by mouth up to once daily as needed, prior to sexual activity. However, even at the lower 5 mg daily dose used for BPH, tadalafil may also be beneficial for erectile dysfunction. Headache and myalgias are the most common adverse effects. Nitrates, such as nitroglycerin or isosorbide dinitrate (Dilatrate-SR, Isordil), are strictly contraindicated in patients taking tadalafil, due to the risk of a drug-drug interaction causing severe hypotension, syncope, and myocardial infarction.

Combination treatment of BPH with both an alpha blocker and a 5-alpha reductase inhibitor can be more effective than either treatment alone. Tadalafil also can be used together with other BPH medications. However, the combination of tadalafil plus an alpha blocker increases the risk of hypotension. Phytotherapy is commonly tried by men with BPH, but no plant extract has been shown to reduce prostate size, improve bladder outlet obstruction, or slow disease progression [7].

Some men who have an overactive bladder due to BPH and obtain only partial symptom relief with the treatments listed above may benefit from the addition of an antimuscarinic medication. Examples include oxybutynin (Ditropan XL), solifenacin (Vesicare), tolterodine (Detrol), and trospium (Sanctura). However, this category of medications can cause urinary retention in men with BPH. They should therefore be used with caution, while closely monitoring symptoms and regularly measuring bladder post-void residual volume. Another medication used for overactive bladder is the beta-3 agonist mirabegron (Myrbetriq).

When a patient with suspected BPH is not improving with pharmacotherapy, consultation with a urologist is recommended. A variety of procedural treatments for BPH can be considered. Prostate size and other factors need to be taken into account. Holmium laser enucleation of the prostate (HoLEP) can be used for prostates of all sizes, even for very large prostates (>100 mL size), so it is gradually replacing the older standard treatment, transurethral resection of the prostate (TURP) [8]. Another advantage of laser technique such as HoLEP and photoselective vaporization of the prostate (PVP) is that they often can be used even in patients at increased risk of bleeding [9].

Prostatitis

Prostatitis is inflammation of the prostate, and it has three main clinical types: acute bacterial prostatitis, chronic bacterial prostatitis, and urologic chronic pelvic pain syndrome (also known as chronic nonbacterial prostatitis). Many patients (and clinicians) think of prostatitis as a prostate infection, but actually less than 10% of prostatitis is due to acute or chronic bacterial infection. Most cases of prostatitis are nonbacterial. A fourth (also uncommon) category is asymptomatic prostatitis, diagnosed when histologic evidence of inflammation is found on prostate biopsy or prostatectomy. Symptomatic prostatitis is common, occurring in 35–50% of men at some time in their lives. A 2015 population study of 10,617 men showed 8.2% had prostatitis symptoms [10].

Acute Bacterial Prostatitis

Acute bacterial prostatitis is essentially an acute bacterial urinary tract infection (UTI) that affects

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the prostate. It can occur in males of any age but is most typical in adult men, with an increased frequency in men age ≥65. Less than 1% of cases of prostatitis are acute bacterial prostatitis [11]. Most occur after a bladder catheterization, transrectal prostate biopsy, or other urinary tract instrumentation. Other factors that increase the risk for bacterial prostatitis include diabetes and the presence of BPH with urine retention.

Typical symptoms of acute bacterial prostatitis are fever, dysuria, urinary urgency and frequency, slow urinary stream, a sense of incomplete bladder emptying, hematuria, chills, pain in the suprapubic or groin areas (which may radiate to the testes or penis), nausea, and vomiting. Physical exam findings commonly include fever and an enlarged and tender boggy prostate. Do not perform an aggressive prostate examination or prostate massage; it can trigger acute clinical decompensation. The differential diagnosis includes sexually transmitted infections and pyelonephritis. Be sure to assess men with fever and dysuria for kidney tenderness; if they do not have pyelonephritis, 90% of these men will have bacterial prostatitis [12].

Urinalysis usually shows leukocyte esterase, and depending on the bacterial cause, may be nitrite positive. (*E. coli* and other members of the Enterobacteriaceae family are the bacteria most likely to be able to convert urinary nitrate to nitrite.) Urine microscopic evaluation may show white blood cells, bacteria, and/or red blood cells. Send a urine culture before starting antibiotics. Remember to also test for sexually transmitted infections when indicated by history or physical findings. The most common bacterial causes of acute prostatitis are uropathogenic strains of *E. coli* (causing 65–80% of cases), Klebsiella and other Enterobacteriaceae, Pseudomonas, and Enterococci. Acute prostatitis can be caused by *Staphylococcus saprophyticus*; this usually occurs in older men. Avoid checking PSA in men who have bacterial prostatitis; the PSA will usually be elevated and remain so for several months, but this elevation just reflects the presence of prostate inflammation and is not helpful in the acute setting. Measure bladder PVR volume with ultrasound; acute urinary retention may be present. Other imaging is usually not needed for men with an initial episode of acute prostatitis that responds to treatment.

Treat bacterial prostatitis with an antibiotic that penetrates the prostate, such as ciprofloxacin (Cipro) 500 mg twice daily, levofloxacin (Levaquin) 750 mg once daily, or trimethoprim/sulfamethoxazole (Bactrim) DS twice daily. Nitrofurantoin (Macrobid) does not penetrate the prostate and should not be used. Treatment duration for acute bacterial prostatitis is usually at least 14 days, although some experts recommend treating for 4–6 weeks [13]. Patients with urinary retention may require catheterization. Adjust the antibiotic choice based on urine culture results. Some patients will be acutely ill and need inpatient management and parenteral antibiotics. Potential complications of acute prostatitis include urosepsis and prostate abscess. Sepsis is more likely in men who are elderly, immunocompromised, or have diabetes or urolithiasis.

Chronic Bacterial Prostatitis

Some men will develop chronic bacterial prostatitis, which is characterized by repeated episodes of UTI symptoms associated with positive urine cultures, usually growing the same bacterial strain each time. Chronic bacterial prostatitis is uncommon, occurring in about 5% of those men who have an initial episode of acute bacterial prostatitis [14]. Symptoms may be similar to acute prostatitis or may be subacute; some patients may present without fever. On digital rectal exam, the prostate is typically enlarged, tender, and boggy. Urine test results will be similar to the details listed above for acute prostatitis. Uropathogenic strains of *E. coli* are the most common bacteria isolated. Imaging tests useful in men with chronic bacterial prostatitis include ultrasound measurement of bladder PVR volume to assess for urine retention, and CT imaging of the abdomen and pelvis to rule out urolithiasis; these problems can cause recurrent infections.

Treat chronic bacterial prostatitis with antibiotics that penetrate the prostate, such as ciprofloxacin, levofloxacin, or trimethoprim/sulfamethoxazole, similar to the treatment for acute prostatitis. Use

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the urine culture to guide antibiotic selection. Most experts recommend a prolonged course (4–6 weeks) of antibiotic therapy for men with documented chronic bacterial prostatitis, and some recommend treating for up to 12 weeks in an attempt to eradicate the infection. Management of comorbid conditions such as urine retention and diabetes can reduce the risk of recurrent infections. When the urine cultures are negative, the patient likely has chronic nonbacterial prostatitis (see below), and antibiotics are not indicated.

For men who have recurrent urinary tract infections, consider consultation and further evaluation by a urologist. Cystoscopy may be needed to assess for problems such as a bladder stone or bladder diverticula. When urine cultures repeatedly show mixed bacterial infections, or when each infection presents with a different type of bacteria, consider if there might be a fistula between the colon and the bladder; diverticulitis is the most common cause.

Chronic Nonbacterial Prostatitis

The most common type of prostatitis is nonbacterial, accounting for 90–95% of cases. The current terminology for this entity is chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CNP/CPPS). CNP/CPPS is often considered together with interstitial cystitis/bladder pain syndrome, under the umbrella term urologic chronic pelvic pain syndrome (UCPPS). The etiology is unclear, but affected patients often have a lower pain threshold than healthy individuals. They typically experience both voiding symptoms and pain, although these are only somewhat correlated. Symptom flares are common and vary in intensity, duration, and impact on quality of life [15].

The evaluation for chronic nonbacterial prostatitis is the same as described above for bacterial prostatitis. However, antibiotics should not be used if urine cultures are negative. Treatment is focused on symptom relief, and satisfaction may be difficult to achieve. Alpha blockers (as described above in the section on "Lower Urinary Tract Symptoms") may improve voiding symptoms. Analgesics such as ibuprofen and other nonsteroidal anti-inflammatory drugs are often used to manage the pain. Some patients respond to centrally acting pain medications such as amitriptyline (Elavil) and pregabalin (Lyrica). Counseling may help with the psychosocial aspects of chronic pain. Nonpharmacologic approaches such as pelvic floor physical therapy, regular exercise, and acupuncture can provide relief for some patients. Consultation with a urologist or chronic pain specialist is recommended for patients with persistent symptoms [16].

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Prostate Cancer

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Introduction

Prostate cancer is the third most common cancer in the United States, and the most common cancer in American men, with an estimated 1,600,000 cases and 29,000 deaths in 2018 [1]. It is an adenocarcinoma that grows in the glandular tissue of the prostate, mostly in the peripheral zone. Prostate cancer has no specific symptoms. Patients may

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present with lower urinary tract symptoms, gross or microscopic hematuria, or hematospermia, but these symptoms and signs also occur in benign conditions. Most cases of prostate cancer are diagnosed using prostate-specific antigen (PSA)-based screening.

Screening

Using PSA to screen for prostate cancer has been controversial for many years due to the risks of both overdiagnoses, resulting in unnecessary invasive or expensive procedures such as prostate biopsy or magnetic resonance imaging (MRI) and overtreatment, resulting in significant quality of life issues such as urinary incontinence, erectile dysfunction, or gastrointestinal complications. Since 2012 the United States Preventive Services Task Force (USPSTF) had recommended against prostate cancer screening using PSA for those reasons, giving it a Grade D recommendation. However, in 2018 their recommendation shifted to Grade C [2], largely influenced by the 13-year follow-up results of the European Randomized Study of Screening for Prostate Cancer (ERSPC), which confirmed a substantial reduction in prostate cancer mortality attributable to PSA screening [3].

The USPSTF recommends PSA-based screening for men age 55 to 69 years after a careful decision-making process but still advises against it for men age 70 years or older [2]. The American Urological Association (AUA) has the same recommendations as USPSTF in terms of age range, and they recommend screening every 2 years, rather than annually, to reduce harms [4]. The American Cancer Society (ACS) recommends routine PSA screening starting at age 50 and starting at age 45 for African-American men and men who have a first-degree relative diagnosed with prostate cancer at an early age (younger than age 65) [5].

Routine PSA screening requires a thorough shared decision-making process. African-American men are at higher-than-average risk for prostate cancer, as are men whose family members have had prostate cancer.

African-American Men

The USPSTF currently does not specify a screening guideline for African-American men due to a lack of direct evidence, but clinicians may consider screening using shared decision-making for this group [2]. The AUA guideline states that clinicians may consider PSA screening for African-American men age 40 to 55 years after discussing the potential benefits and harms [4]. The ACS recommends clinicians discuss PSA screening with African-American men at age 45 years [5].

Family History of Prostate Cancer

The USPSTF currently does not specify a screening guideline for patients with a family history of prostate cancer due to a lack of direct evidence, but clinicians may consider screening using shared decision-making for this group [2]. The AUA has the same recommendations for patients with a family history of prostate cancer as for African-American men [4]. Interestingly, the ACS further specifies a screening guideline for this group. ACS recommends clinicians discuss PSA screening from age 45 for men with a first-degree relative (father or brother) diagnosed with prostate cancer at an early age (younger than age 65) and from age 40 for men at appreciably higher risk (multiple family members diagnosed before age 65 years) [5]. Researchers currently are investigating the role of prostate cancer screening for patients with familial cancer syndromes such as BRCA1, BRCA2, and mismatch-repair mutations, as in Lynch syndrome.

Interpreting Prostate-Specific Antigen

PSA is a "prostate-specific" marker, but it is not "prostate cancer specific." Please see Table 1 that summarizes the benign conditions and procedures that are associated with PSA elevation. A threshold PSA value of 4.0 ng/mL has been most widely accepted standard cutoff between normal and abnormal. There have been studies of lowering the PSA cutoff down to 3.0 ng/mL or 2.5 ng/mL

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Table 1 Benign conditions and procedures associated with PSA elevation

Acute or chronic bacterial prostatitis
Acute urinary retention
Aging
Benign prostatic hyperplasia
Chronic prostatitis/chronic pelvic pain syndrome
Digital rectal examination
Ejaculation
Prostate biopsy
Prostatic massage
Rigid cystoscopy
Transurethral resection of the prostate
No association
Non-traumatic urethral catheterization
Diagnostic flexible cystoscopy

for early detection, but doing so increases the risks of overdiagnosis and overtreatment of clinically insignificant prostate cancers [6]. The AUA does not recommend a single threshold PSA value to prompt a prostate biopsy, noting that risks exist at any PSA level [7].

Family physicians should be careful in interpreting PSA when a patient is on a 5-alpha reductase inhibitor such as finasteride or dutasteride, because these medications lower the PSA by about 50% when used over 12 months [8]. Therefore, it is suggested that measured PSA values need to be doubled when interpreting the level for a patient who has been on a 5-alpha reductase inhibitor for more than 12 months.

There also have been suggested PSA derivatives to help prostate cancer detection, such as age-specific PSA, free/total PSA ratio, complex PSA, PSA density, and PSA velocity. It is still unclear if these PSA derivatives are of clinical significance. It is helpful to know that a typical cutoff for PSA velocity (rise in PSA over time) is 0.75 ng/mL/year. The AUA guideline states that PSA derivatives should be considered secondary tests, not primary screening tests with potential utility for determining prostate biopsy [9].

Role of Digital Rectal Examination

Digital rectal examination (DRE) looking for a hard prostate nodule used to be the traditional method for screening for prostate cancer. The USPSTF does not recommend DRE as a screening tool due to lack of evidence [2]. The AUA guideline states that DRE should be considered as a secondary test, not a primary screening test with potential utility for determining prostate biopsy [9]. A 2018 systematic review and meta-analysis concluded that routine DRE as a prostate cancer screening test in the primary care setting should be discouraged, given the considerable lack of evidence [10]. On the other hand, there is evidence that DRE in conjunction with PSA testing enhances the prostate cancer detection rate [11]. Therefore, even though DRE is not a routine screening method, it should be considered as a secondary tool if prostate cancer is clinically suspected.

Diagnosis

Prostate Biopsy

If prostate cancer is suspected, patients should be referred for a core needle prostate biopsy, which is typically an outpatient procedure done with local or regional anesthesia. A 12-core transrectal ultrasound (TRUS)-guided biopsy is the most commonly performed standard approach. Another method is fusion biopsy, which uses computer software to electronically fuse magnetic resonance images of the prostate with ultrasound images to guide the biopsy; fusion biopsy has been used to further enhance the prostate cancer detection rate [12]. In some centers, transperineal prostate biopsy is increasingly used due to lower rates of infection and better access to the anterior prostate than the transrectal approach.

Staging and Risk Stratification

Family physicians are encouraged to be familiar with prostate cancer staging and risk stratification, which are based on the number of positive biopsy cores, the PSA level, clinical stage, and the Gleason score. All of these factors are fundamental for choosing treatment options. Gleason scores range from 6 to 10, with higher

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numbers indicating a more aggressive cancer; the score is determined by the pathologist who examines the biopsy samples. Grade Group is a related method that scores prostate cancer aggressiveness from 1 to 5, with 5 being the most aggressive. Please see below for summaries of the clinical tumor-nodes-metastases (TNM) staging and risk stratification methods [13, 14] (Tables 2 and 3).

Role of Magnetic Resonance Imaging

Family physicians may be asked by patients about the role of MRI in prostate cancer. Prostate MRI is primarily and conventionally used when staging unfavorable intermediate risk to very high risk biopsy-proven prostate cancer. The AUA guideline states that MRI should not be performed for very low risk or low-risk disease [15]. However, multiparametric MRI (mpMRI) of the prostate has had an increasingly important role. It consists of conventional T1 and T2 MRI sequences, supplemented by diffusion-weighted, dynamic contrast-enhanced, and spectroscopic imaging. Given the evidence that MRI/ultrasound fusion biopsy increases the prostate cancer detection rate [12], the mpMRI is increasingly used as a tool for doing fusion biopsies for patients with a previous negative biopsy but a persistently elevated PSA and for patients who are on active surveillance to look for high-grade prostate cancer. However, prostate MRI should not be used for routine primary screening for prostate cancer. The AUA guideline states that MRI can be considered as a secondary test with potential utility for determining prostate biopsy [9].

Table 2 Clinical TNM staging of prostate cancer

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Clinically inapparent tumor neither palpable nor visible by imaging
T1a: Tumor incidental histologic finding in 5% or less of tissue resected
T1b: Tumor incidental histologic finding in more than 5% of tissue resected
T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2: Tumor confined within prostate
T2a: Tumor involves one-half of one lobe or less
T2b: Tumor involves more than one-half of one lobe but not both lobes
T2c: Tumor involves both lobes
T3: Tumor extends through the prostate capsule
T3a: Extracapsular extension (unilateral or bilateral)
T3b: Tumor invades seminal vesicle(s)
T4: Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Regional lymph nodes (N)
NX: Regional lymph nodes were not assessed
N0: No regional lymph node metastasis
N1: Metastasis in regional lymph node(s)
Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis
M1a: Nonregional lymph node(s)
M1b: Bone(s)
M1c: Other site(s) with or without bone disease

Source: American Joint Committee on Cancer: Prostate Cancer Staging, 7th Edition. Available at: https://cancerstaging.org/references-tools/quickreferences/Documents/ProstateSmall.pdf. Accessed 2/29/2020

Atypical Lesions on Biopsy

Sometimes atypical lesions are found on prostate biopsy which are not fully confirmed malignant. Two commonly encountered atypical lesions are high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP). Given that the risk of prostate cancer following the diagnosis of HGPIN is 20–30%, which is not significantly higher than that after a benign biopsy, and most of the cancers found after previous HGPIN are Gleason 6 (grade group 1), men with single-core HGPIN do not need a routine repeat prostate biopsy [16]. If HGPIN is multifocal, monitoring with serum and urine markers and/or imaging such as mpMRI may be warranted. In contrast, ASAP has about 20% risk of higher Gleason score (>7) prostate cancer, which mandates careful monitoring and may warrant repeat prostate biopsy in selected patients [16].

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Table 3 Risk stratification of clinically localized prostate cancer

Very low risk
Clinical stage of T1c *AND* Grade group 1 *AND* PSA < 10 ng/mL *AND* Fewer than 3 biopsy fragments/cores positive, ≤ 50% cancer in each fragment/core *AND* PSA density < 0.15 ng/mL/g
Low risk
Clinical stage of T1 to T2a *AND* Grade group 1 *AND* PSA < 10 ng/mL
Intermediate risk
Clinical stage of T2b to T2c *OR* Grade group 2 (favorable) or group 3 (unfavorable) *OR* PSA 10–20 ng/mL
High risk
Clinical stage of T3a *OR* Grade group 4 or 5 *OR* PSA > 20 ng/mL
Very high risk
Clinical stage of T3b to T4 *OR* Primary Gleason pattern 5 *OR* > 4 cores with grade group 4 or 5 Grade group 1: Any Gleason score ≤ 6 Grade group 2: Gleason score 3 + 4 = 7 Grade group 3: Gleason score 4 + 3 = 7 Grade group 4: Any Gleason score 8 (3 + 5, 4 + 4, or 5 + 3) Grade group 5: Any Gleason score 9 or 10 (4 + 5, 5 + 4, or 5 + 5)-

Source: NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 3/10/2020

Treatment

Treatment of prostate cancer largely depends on risk stratification, as summarized in the Risk Stratification of Clinically Localized Prostate Cancer above. The AUA guideline states that patients with very low-risk or low-risk prostate cancer should be offered active surveillance as an initial option. Definitive treatment such as radical prostatectomy or radiotherapy can be considered for selected low-risk patients who have a risk of disease progression. Androgen-deprivation therapy should not be recommended to very low-risk or low-risk patients. For those who have intermediate-risk prostate cancer, either radical prostatectomy or radiotherapy (combined with androgen-deprivation therapy) should be considered as an initial treatment modality. For high-risk disease, either radical prostatectomy or radiotherapy (combined with androgen-deprivation therapy) should be the standard initial treatment option. Focal therapy such as cryotherapy or high-intensity focused ultrasound (HIFU) should not be offered for high-risk disease. Also, either radiotherapy alone or androgen-deprivation therapy alone should not be the choice for high-risk disease [15]. More advanced or metastatic prostate cancer should be treated with different anti-androgen or chemotherapeutic regimens, depending on the clinical stage and decision-making [17]. It is important to offer supplemental calcium and vitamin D to help maintain bone health for patients who have metastatic bone diseases. The AUA guideline states that clinicians may

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choose either denosumab (Prolia, Xgeva) or zoledronic acid (Reclast) when considering preventive measures for skeletal-related events to patients with metastatic bone disease [17].

Survivorship

Active Surveillance Vs. Watchful Waiting

Family physicians are encouraged to be familiar with both active surveillance and watchful waiting as these approaches to prostate cancer can be performed in a primary care setting. Active surveillance and watchful waiting may appear similar, but their treatment goals are completely different. Active surveillance focuses on early detection of cases that require definitive treatment such as radical prostatectomy or radiotherapy. However, watchful waiting is mainly intended to maintain quality of life by avoiding unnecessary definitive treatment when prostate cancer is not likely to cause mortality or significant morbidity. Watchful waiting is waiting until the disease progresses or causes symptoms, when appropriate palliative treatment can be performed. Watchful waiting should therefore be offered to patients who have significantly reduced life expectancy.

Protocols for active surveillance and watchful waiting may vary depending on physician preference or health system policy. The National Comprehensive Cancer Network (NCCN) guideline recommends that active surveillance include PSA no more often than every 6 months unless clinically indicated, DRE no more often than every 12 months unless clinically indicated, repeat prostate biopsy no more often than every 12 months unless clinically indicated, and repeat mpMRI no more often than every 12 months unless clinically indicated [14]. Regarding watchful waiting, NCCN recommends both PSA and physical examination no more often than every 6 months, without surveillance biopsies or radiographic imaging. When symptoms develop or are imminent, patients can begin palliative androgen-deprivation therapy [14].

Monitoring after Prostate Cancer Treatment

The American Society of Clinical Oncology (ASCO) recommends measuring serum PSA every 6 to 12 months for the first 5 years after definitive prostate cancer treatment and then annually [18]. Family physicians are encouraged to become familiar with the definition of biochemical recurrence (also called biochemical failure), as explained below. Patients who have a biochemical recurrence after definitive treatment need to be referred back to their original treatment team in a timely manner. Sometimes clinicians miss the diagnosis of biochemical recurrence, misinterpreting the rise in PSA as being within the normal range.

There are important differences between biochemical recurrences in patients who are post-prostatectomy and post-radiotherapy. The AUA defines biochemical recurrence after radical prostatectomy as an initial PSA value $\geq$0.2 ng/mL, followed by a subsequent confirmatory PSA value $\geq$0.2 ng/mL [19]. However, after radiotherapy, AUA uses the 2005 Consensus Committee conclusion in their guideline to define post-radiotherapy biochemical recurrence as a serum PSA $\geq$ 2.0 ng/mL above nadir or 3 consecutive rises in PSA level [20]. (The term "nadir" refers to the lowest PSA attained after radiotherapy.) This definition can be applied to both external beam radiation therapy and interstitial brachytherapy, regardless of whether the radiotherapy was accompanied by androgen-deprivation therapy [20, 21].

In addition, family physicians should be familiar with how to interpret PSA values for patients on androgen-deprivation therapy for metastatic prostate cancer. For these patients, a failure to achieve a PSA nadir of $<$4.0 ng/mL 7 months after androgen-deprivation therapy initiation suggests very poor prognosis, whereas patients with a PSA nadir of $<$0.2 ng/mL have a relatively good prognosis [22].

Quality of Life

Quality of life is a key focus of treatment for patients who have undergone prostate cancer treatment. Erectile dysfunction (ED) occurs in 30–60%

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of patients after radical prostatectomy or radiotherapy. Patients who had radical prostatectomy and lose erectile function may regain it during the 2 years following surgery, whereas radiotherapy typically causes a gradual decline in erectile function during the first 24–36 months after treatment, followed by stabilization or partial recovery. Primary care physicians can offer phosphodiesterase-5 inhibitors such as avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra, Staxyn) as the initial treatment for patients with ED. Patients with persistent sexual dysfunction should be referred to a urologist, sexual health specialist, or psychotherapist [18]. Other treatment options for ED include intracavernosal alprostadil injections (Caverject, Edex), intraurethral alprostadil (Muse), vacuum erectile devices, or penile prosthesis placement.

Most men who undergo radical prostatectomy experience urinary incontinence for the first few months after the surgery. The incontinence usually subsides to become small to no bother by 1 year after radical prostatectomy [15]. Family physicians can refer patients with incontinence to physical therapy for pelvic floor rehabilitation and should instruct such patients on Kegel exercises [18]. For persistent and bothersome incontinence, patients should be referred to a urologist for evaluation and consideration of possible procedures such as male urethral sling or artificial urinary sphincter placement.

Proctitis occurs in less than 10% of patients after radiotherapy for prostate cancer, but it can cause rectal frequency, urgency, loose stools, or rectal bleeding [15]. Primary care physicians can offer these patients stool softeners, topical steroids, or anti-inflammatories as an initial measure but should refer to specialists for persistent symptoms [18].

Mood issues including anxiety and depression should be monitored in prostate cancer survivors. The ASCO recommends managing survivors' distress and depression using in-office counseling resources or pharmacotherapy as appropriate [18]. A 2018 systematic review showed that exercise is effective at improving cardiorespiratory fitness, muscle strength, fatigue, incontinence, physical activity levels, and quality of life [23], so prostate cancer survivors should be encouraged to exercise.

Prevention

Risk Factors

It is important to understand prostate cancer risk factors so that clinicians can better plan preventive strategies. Both genetics and environmental factors are known to play a role in carcinogenesis. The most well-known risk factors are advanced age, African-American ethnicity, and genetic factors (such as BRCA). Obesity, hormonal factors, and a variety of dietary factors have been studied, but their role in carcinogenesis is inconclusive. Currently, there is no evidence that prostatitis, benign prostatic hyperplasia, or vasectomy is associated with prostate cancer.

Chemoprevention

Two key trials have studied the role of 5-alpha reductase inhibitors (finasteride, dutasteride) on prostate cancer prevention: Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE). The PCPT trial concluded that finasteride reduced prostate cancer prevalence by 24.8% over a 7-year period compared to placebo [24]. The REDUCE trial showed that dutasteride reduced prostate cancer risk by 22.8% over a 4-year period compared to placebo [25]. However, both trials found a significantly higher rate of aggressive cancers (those with high Gleason scores) in the 5-alpha reductase inhibitor groups compared to placebo, which was problematic. There currently is no standardized guideline for using 5-alpha reductase inhibitors for prostate cancer chemoprevention.

Dietary factors including soy, lycopene, and green tea have not shown any proven efficacy in prostate cancer prevention. The roles of vitamin E and selenium have been studied, but the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed that neither one prevents

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prostate cancer, and it showed that vitamin E significantly increased the risk of prostate cancer among healthy men [26].

When to Refer to Urology

Patients with any of the following findings should be referred to a urologist:

- Screening PSA $\geq$ 4.0 ng/mL on two or more occasions.
- Screening PSA $\geq$ 2.0 ng/mL on two or more occasions in a patient who has been on a 5-alpha reductase inhibitor (finasteride or dutasteride) for at least 6 months.
- Screening PSA velocity (rise over time) $\geq$ 0.75 ng/mL/year.
- DRE showing a hard prostate nodule.
- PSA $\geq$ 0.2 ng/mL after radical prostatectomy.
- PSA $\geq$ 2.0 ng/mL above nadir after radiotherapy.

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Surgery of the Male Genital Tract

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Karl T. Rew

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Neonatal Circumcision

Neonatal circumcision is controversial, and family physicians should make an effort to fully understand the religious, cultural, medical, and ethical arguments on both sides of the debate in order to provide parents with accurate and unbiased information. Questions to consider include: Should circumcision be done, and if so, when, how, and by whom?

Religious and cultural norms are the primary motivation for most neonatal circumcisions. Ritual circumcision remains nearly universal among Jews and Muslims. In the USA, non-ritual (secular) neonatal circumcision is common, although it is not common in most of the rest of the world. Rates of neonatal circumcision in the USA decreased from 64.5% to 58.3% between 1979 and 2010, with significant regional, ethnic, and racial variation. Circumcision rates are highest in the US Midwest and lowest in the West [1].

Potential medical benefits of circumcision include a reduction in urinary tract infections during the first year of life. There also is evidence that circumcision reduces the subsequent risk of heterosexual acquisition of HIV for those living in high-risk areas and may reduce the transmission of other sexually transmitted infections. Potential harms of circumcision include acute complications such as pain, bleeding, infection, and injury to the glans of the penis, as well as later complications that may need surgical management, such as meatal stenosis, skin bridges, or redundant foreskin leading to an uncircumcised appearance. The effects of circumcision on adult penile sensation and sexual satisfaction are unclear but vigorously debated.

Ethical issues related to circumcision include the patient's autonomy and right to bodily integrity. This consideration advocates for decisions

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regarding circumcision to be made by the person undergoing the procedure when he is old enough to give consent, rather than by his parents. In much of the world outside the USA, neonatal male circumcision is increasingly seen as a needless and harmful human rights violation, just as is female genital cutting [2]. However, in the USA, weighing the risks and benefits of this decision is generally left up to the parents.

An influential 2012 policy statement from the American Academy of Pediatrics recognizes some of the controversy surrounding circumcision, pointing out that, "Although health benefits are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it." [3] The American Academy of Family Physicians 2018 policy statement on neonatal circumcision uses similar but somewhat less supportive language [4]. Outside the USA, support for non-ritual neonatal circumcision is uncommon. In the United Kingdom, circumcision is considered to have essentially no medical benefit and is not covered by insurance. In the Netherlands, circumcision is not only considered to have no medical benefit but also is seen as causing physical and psychological trauma [5].

About half of circumcisions in the USA are performed during the neonatal period, defined as the first 30 days of life. At this age, the cost of the procedure is lower because most circumcisions can be done under local anesthesia, and suturing is typically not needed. Most non-ritual neonatal circumcisions in the USA are performed by the physicians immediately involved in the birthing process, including family physicians, pediatricians, and obstetricians. After the neonatal period, urologists perform the majority of circumcisions [6].

Physicians have a duty to provide clear, accurate, and unbiased information for parents who are considering circumcising their newborn son, and physicians should respect the parents' decision. It is worthwhile having this discussion even before the child is born. Informed consent must be obtained prior to the procedure. For families who choose a natural penis, advise them that a tight foreskin (physiological phimosis) is normal in young boys and instruct them to avoid forceful retraction of the foreskin, especially in the first year of life.

When evaluating a newborn male whose parents are requesting circumcision, the next important element is to assess for contraindications. Candidates for neonatal circumcision should be healthy, at least 12 h old, and have urinated at least once. Examine the genitalia carefully. Micropenis (stretched length $\leq$1.9 cm), concealed penis, and ambiguous genitalia are contraindications. Premature infants are often not candidates due to small penis size. Infants with anatomic abnormalities that may require surgical repair should not undergo neonatal circumcision. These conditions include hypospadias, epispadias, chordee, and webbed or buried penis. Sometimes hypospadias or another abnormality is discovered after a dorsal slit is performed during circumcision; in that situation, the procedure should be stopped and the patient referred for a urology consultation. Infants with bleeding disorders such as hemophilia or thrombocytopenia should not undergo neonatal circumcision [7].

Circumcision at any age is an invasive and painful procedure, so anesthesia is necessary. Local anesthesia is usually sufficient for neonatal circumcision. Ring block or dorsal penile nerve block using lidocaine are the preferred approaches. Lidocaine with epinephrine should never be used because the vasoconstrictive properties of epinephrine increase the risk of ischemia and tissue necrosis. Topical anesthesia with EMLA cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is less effective alone but improves pain relief when used in combination with a ring block or dorsal penile nerve block [8].

The most common instruments used for neonatal circumcision in the USA are the Gomco clamp, the PlastiBell device, and the Mogen clamp. The choice depends on the clinician's training and preference. Outcomes are similar, with some variation in risk of complications. The most important element is the skill of the operator. The Gomco and Mogen clamps are reusable metal devices. The PlastiBell device is disposable, comes in a range of sizes (the correct size must be selected), and is left in place after the

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procedure. The Gomco clamp and PlastiBell device require a dorsal slit. Detailed procedural guidelines are beyond the scope of this chapter but can be found elsewhere [9]. In some cases, absorbable sutures may be needed to control bleeding. If suturing ventrally, take care to avoid the urethra. If bleeding persists, clotting studies are indicated.

Instruct parents to watch for bleeding or evidence of infection. Provide them with printed postprocedural instructions. Parents should apply petrolatum jelly (Vaseline) to the front of the diaper to help prevent the healing area from sticking to the diaper. Acetaminophen can be used for pain relief if needed. The PlastiBell device, if used, should fall off within a week. Surgical follow-up can generally be done at the next well-child visit.

Undescended Testis

Before birth, the testes of a male fetus develop along the posterior abdominal wall near the kidneys, and they later descend from the abdomen, eventually moving through the inguinal canal and then into the scrotum around 25–30 weeks of gestation. At the time of birth, undescended testis, or cryptorchidism, is present in 2–4% of full-term newborn males; in preterm males, the rate is 20–30%. In about a third of cases, both testes are undescended. The etiology is unclear but probably multifactorial. Male infants whose father or brother had an undescended testis are at higher risk, and other genetic, hormonal, and environmental factors likely contribute to the risk. Spontaneous resolution is common during the first few months of life, so that by age 12 months, the prevalence of undescended testis has decreased to about 1% [10].

The potential complications associated with undescended testis include infertility and testicular cancer. The risk of testicular torsion is also increased; torsion is discussed in more detail later in this chapter. One reason males with a history of undescended testis are at risk for infertility or subfertility appears to be that an undescended testis is exposed to an environment that is too warm. Abdominal temperature is higher than scrotal temperature, and for optimal testicular germ cell development and successful spermatogenesis, an ambient temperature that is lower than abdominal temperature is needed. Fertility is most likely to be affected in males with bilateral undescended testes, or if treatment is delayed. For the best results regarding future fertility, the undescended testis should be brought into the scrotum between ages 6 and 18 months. Undescended testis is also the most important known risk factor for testicular germ cell tumors. The cause for this association is unclear. Definitive early treatment of undescended testis appears to provide the most effective reduction in the patient's future risk of testicular cancer [11]. The American Urological Association (AUA) recommends urology consultation at age 6 months and surgical treatment by age 18 months [12].

Physical exam is the most reliable method of diagnosing undescended testis. Ultrasound or other imaging is not necessary. Examine the genitalia at each well-child visit. An effective approach is to place the patient in a supine frog leg position. Inspect the penis and urethral opening. Palpate the scrotum on each side. If a testis is not palpable in the scrotum, palpate the inguinal canal. If the testis is still not palpable, start at the anterior superior iliac spine and use fingers to sweep the inguinal area down towards the scrotum. About 70% of undescended testes are palpable, and most will be in the inguinal canal [12]. Testes that are descended but retractile can be delivered into the scrotum by gradually stretching the cremasteric muscle [13]. Retractile testes typically do not require surgical intervention but should be monitored annually with a physical exam for possible secondary ascent. If the diagnosis is unclear on physical exam, consult a urologist. If bilateral undescended testes are noted on a newborn exam, look for hypospadias or other genital abnormalities; when present, promptly refer the patient to a pediatric urologist. Genital ambiguity with bilateral undescended testes could indicate a genetic female with virilization, which can occur with congenital adrenal hyperplasia or a disorder of sexual differentiation, such as intersex.

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If the genitalia of a newborn male with undescended testis otherwise appear normal, the recommended initial management is 6 months of watchful waiting. If one or both testes remain undescended by age 6 months, refer the patient to a pediatric urologist so that definitive treatment can be accomplished before age 18 months. (For preterm infants, use corrected age, rather than chronological age. For example, a 6-month-old infant who was born 2 months early has a corrected age of 4 months.)

In the USA, the recommended treatment for a palpable undescended testis is orchiopexy (an alternative spelling is orchidopexy), which is a surgical repositioning of the testis and fixing it in the scrotum [13]. Approaches to treatment that use hormonal manipulation via repeated injections in an attempt to induce testicular descent are not recommended due to low response rates and lack of evidence for long-term efficacy [12].

If an undescended testis is not palpable, it might be in the abdomen, or it might be atrophic (typically due to prenatal torsion), or absent (anorchia). When a testis is not palpable, exploration and orchiopexy are usually performed laparoscopically. If a nonpalpable undescended testis not found in the abdomen, it is generally assumed to have undergone prenatal torsion; orchiopexy is then typically done on the contralateral testes to minimize the future risk of torsion on that side. An undescended testis is often associated with a patent processus vaginalis, so most patients have an inguinal hernia or hydrocele that will need to be repaired at the time of orchiopexy.

A history of undescended testis increases the risk of testicular cancer, even after prepubertal orchiopexy. Compared to other cancers, testicular cancer is not common, accounting for about 1% of cancers in men and occurring in about 1 in 250 males at some point during their lifetimes. Treatment is very effective at all stages [14]. Evidence does not support screening for testicular cancer in the general population. However, because males who had an undescended testis are at increased risk of testicular cancer, the American Urological Association recommends instructing them to do monthly testicular self-exams beginning at puberty to facilitate early detection [12].

Testicular Torsion

Testicular torsion occurs when the spermatic cord twists, blocking blood flow to the testis. This is a surgical emergency for which rapid recognition and treatment are essential. Irreversible changes due to ischemia in the affected testis start within hours. Testicular salvage rates are 90–100% if surgery is done within 6 h of symptom onset, but fall to about 50% after 12 h, and are less than 10% after 24 h [15].

Torsion can occur at any age but is more common in younger males, with two peaks in incidence: one during the first year of life and another around age 12–13 years that is thought to be associated with the increase in testicular size at puberty [16]. Males with undescended testis are at increased risk for torsion, as are with those a family history of torsion. In some patients, torsion occurs after trauma. Infant perinatal torsion may be extravaginal, but postnatal and later (adolescent) torsion is usually intravaginal, which means that the twisting occurs within the tunica vaginalis. A common finding on surgical exploration is the bell-clapper deformity, where the testicular attachment to the tunica vaginalis is abnormal, allowing easier rotation of the testis [17]. The bell-clapper deformity may be bilateral, and in some patients, it can lead to intermittent torsion with episodic testicular pain.

Torsion is diagnosed by history and physical exam. Classic symptoms include sudden severe unilateral scrotal pain, often with nausea and vomiting, but without dysuria or other urinary symptoms. On exam, the affected testis is usually high-lying. About half of affected testes will have a transverse (horizontal) lie, where the normal position would be vertical. An absent cremasteric reflex means torsion is likely. Scrotal swelling and erythema may be present. Torsion of the appendix testis causes pain and focal tenderness in the upper pole of testis, and a tender blue dot may be visible through the scrotal skin; this problem does not require surgical treatment [18]. The differential

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diagnosis for acute scrotal pain includes infectious causes such as epididymitis and orchitis, where pain and tenderness are common, urinary symptoms and fever may be present, but the cremasteric reflex is usually normal. If the diagnosis is unclear, consult a urologist. Color Doppler ultrasound can confirm a diagnosis of torsion, but clinicians should never postpone surgical treatment to wait for ultrasound. Laboratory tests are rarely needed.

If the physical exam is consistent with torsion and surgical management will be delayed, manual detorsion can be considered. With the patient lying in a supine frog leg position and the examiner at the patient's feet, manual detorsion is traditionally attempted clockwise for the left testis (on the examiner's right) and counterclockwise for the right testis (on the examiner's left). These directions of motion, often described as "opening a book," will only be correct for reversing torsion in about two-thirds of cases, and in the other one-third will make it worse. Manual detorsion causes significant discomfort; however, success results in prompt pain relief that confirms the diagnosis. The number of twists present in a torsed testis ranges from a half twist (180°) to 3 full twists (1080°), although the most common is 1 full twist (360°) to 1.5 twists (540°). Residual torsion is present in about 27% of cases after attempted manual detorsion [19].

In all cases, whether an attempted detorsion appears successful or not, urology consultation is required for immediate surgical exploration, detorsion, and bilateral orchiopexy. Completing an orchiopexy on the unaffected contralateral testis helps minimize the risk of future torsion on that side. A midline transscrotal approach is usually adequate for this type of surgery. Orchiectomy will be needed if the affected testis is not viable. Testicular salvage rates are minimal for patients with neonatal torsion. For patients who require orchiectomy, later placement of a testicular prosthesis is an option for cosmetic purposes. After torsion, the affected testis may become atrophic, even when the patient has received timely surgical treatment. Additionally, future fertility can be impaired, [20] although testicular hormonal function is likely to remain intact. Because testicular injury due to sports participation is rare, males with a single testis can participate in contact sports. However, it is reasonable to counsel them to use a scrotal protective cup [21].

Vasectomy

Vasectomy is the most effective form of contraception available for men. For couples in the USA, it is currently the fifth most popular method after oral contraceptives, tubal ligation, condoms, and long-acting reversible contraceptive methods such as intrauterine devices and hormonal implants [22]. Vasectomy is safer, less expensive, and more effective than tubal ligation. However, it is less widely used: about 6.6% of US men ages 18–45 years have had a vasectomy, while 16.4% of women in the same age range have undergone tubal ligation [23]. Approximately 525,000 vasectomies were performed in the USA in 2015, about 82% of them by urologists [24].

Pre-vasectomy counseling is important. Although vasectomy should be seen as a permanent form of contraception, about 20% of men who have had vasectomy express a desire for more children, and 1.9% will undergo vasectomy reversal [23]. Men considering vasectomy should therefore be advised to think carefully about whether they might want to have children in the future, particularly if their circumstances were to change. Men who chose to have a vasectomy in their 20s are significantly more likely to later undergo vasectomy reversal than men who were 30 years or older at the time of their vasectomies [25]. About 10% of couples will express regret after sterilization [23]. For men who have had a vasectomy, regret is most common when they are in a new relationship after separation, divorce, or death of a former partner [26].

The AUA vasectomy guideline [27] recommends that pre-vasectomy counseling cover the following topics:

- Vasectomy is intended to be permanent.
- Other permanent and nonpermanent alternatives are available.

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- Options for fertility after vasectomy include surgical reversal and sperm retrieval, but these approaches are expensive and are not always successful.
- Vasectomy does not produce immediate sterility.
- After vasectomy, another form of contraception is necessary until successful vas occlusion is confirmed with a post-vasectomy semen analysis.
- Even when vas occlusion is confirmed, vasectomy is not 100% reliable in preventing pregnancy.
- The risk of pregnancy after vasectomy is 1 in 2000 if the post-vasectomy semen analysis is negative (showing zero sperm or rare nonmotile sperm).
- Repeat vasectomy is occasionally necessary (in less than 1% of cases).
- Chronic scrotal pain occurs in 1–2% of men after vasectomy.
- The surgical complication rate is 1–2%; the most common complications include symptomatic hematoma and infection.
- Patients should refrain from ejaculation for approximately 1 week after vasectomy.

During the pre-vasectomy visit, assess for contraindications. Men who have uncontrolled coagulation disorders should not undergo vasectomy. A bacterial infection of the scrotum is also a contraindication. Before the procedure, make sure the patient has reasonable expectations and does not expect the vasectomy to resolve conflict in a relationship or cure sexual problems. Obtain informed consent.

When examining a patient who is considering vasectomy, perform a thorough genital exam. Palpate the scrotum, making sure both testes are normal and that the vas deferens is clearly palpable on both sides and can be elevated. Assess for inguinal hernia, hydrocele, and varicocele. Do not proceed if the patient is too anxious, has excessive scrotal sensitivity, or otherwise cannot tolerate the exam.

For most men, no laboratory testing is needed prior to vasectomy. Antiplatelet medications and warfarin (Coumadin) should be stopped 5–7 days prior to vasectomy and not restarted for 2–3 days afterward. Most direct oral anticoagulants should be stopped 2 days before the procedure and can usually be restarted after adequate hemostasis is attained. If in doubt, consult a coagulation specialist.

Detailed procedural guidance is beyond the scope of this chapter but can be found elsewhere [27, 28]. Local anesthesia administered either using a jet injector or a syringe and small gauge (25–32 gauge) needle is appropriate for most patients. The no-scalpel technique (which uses a sharp pointed hemostat) or a similar minimally invasive technique is recommended for accessing and isolating each vas. A single scrotal incision is usually sufficient. Three main approaches to occluding the vas have been shown to be effective and are commonly used in the USA.

1. Mucosal cautery with fascial interposition.
2. Mucosal cautery without fascial interposition.
3. Open ended vasectomy, which leaves the testicular end of the vas unoccluded, and uses mucosal cautery and fascial interposition on the abdominal end.

There are many variations on these methods. Clips and ligatures are used by some surgeons but are not required. Some surgeons routinely excise a short (about 1 cm) section of the vas, but this is also not required. The surgeon's training and experience with the selected method are the keys to consistent and satisfactory results [27].

Sending an excised portion of the vas for routine histologic analysis adds additional expense and is not necessary. Instead, a single post-vasectomy semen analysis is typically sufficient to ensure effectiveness. Motile sperm are usually cleared from the semen by 6 weeks after vasectomy. Perform the semen analysis 8–16 weeks after the vasectomy. Although a routine post-procedural physical examination is not usually needed, scheduling an appointment for the semen analysis improves the likelihood it will be completed. Instruct the patient to collect a fresh specimen via masturbation. Analyze the undiluted, uncentrifuged specimen within 2 h of collection, examining at least 50 high-power

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fields looking for motile or nonmotile sperm. A negative semen analysis is defined as no motile sperm and rare nonmotile sperm (meaning ≤100,000 nonmotile sperm per mL). If the semen analysis is negative, it does not need to be repeated. If it is positive, instruct the patient to continue to use another method of contraception, and repeat the semen analysis at intervals of 4–6 weeks. If motile sperm are still present 6 months after vasectomy, the vasectomy has failed; this result may represent recanalization. Repeat vasectomy should be considered [27].

Swelling, bruising, and discomfort are common adverse effects of vasectomy that usually resolve without intervention. The main potential acute complications of vasectomy include hematoma, scrotal infection, and abscess formation. These occur in 1–2% of patients. Additionally, about 1–2% of patients will develop post-vasectomy pain syndrome, with chronic scrotal or pelvic pain; however, surgical management is rarely necessary. Initial treatment options include nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, nerve blocks, gabapentin (Neurontin), as well as acupuncture and other complementary approaches. Surgical vasectomy reversal is used in some cases to manage post-vasectomy pain syndrome due to epididymal congestion, but it is not always successful in resolving the pain, and may restore fertility [29]. Another treatment for post-vasectomy pain is surgical removal of the epididymis (epididymectomy); this is technically easier than vasectomy reversal and leaves the patient sterile.

Although vasectomy is a simple and effective procedure, vasectomy reversal (vasovasostomy or vasoepididymostomy) is a technically challenging procedure usually not covered by insurance, and it is only 30–76% effective at restoring fertility [25]. Another option for post-vasectomy men who desire fertility is in vitro fertilization via intra-cytoplasmic sperm injection, which can use sperm harvested from the testis or epididymis. This approach to restoring fertility also is complex, expensive, and may not be covered by insurance. Pre-vasectomy sperm cryopreservation is a less costly option, although annual storage fees will add up over time. Men who are uncertain about their future plans for having children should not undergo vasectomy and should use an alternate form of contraception.

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Selected Disorders of the Genitourinary System

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Diane Holden and Paul Crawford

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Scrotal Mass

Some genitourinary (GU) disorders present as a scrotal mass and are commonly seen by family physicians for initial evaluation and management. These nontesticular masses include hydrocele, varicocele, indirect hernia, spermatocele, and epididymitis and testicular masses such as testicular

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cancer. A clinically useful distinction can be made between painful and painless scrotal masses. Although painless masses are not uniformly benign, painful masses are much more likely to require urgent intervention.

Normal testes are firm but not hard, nearly equal in size, smooth, and ovoid. Normal testicular length ranges from 1.5 to 2 cm before puberty and from 4 to 5 cm after puberty. The epididymis is posterolateral to the testicle; the epididymis and testicle are separate but attached. The vas deferens emanates from the tail of the epididymis and joins the vascular pedicle of the testicle to form the spermatic cord. The spermatic cord travels superiorly to the inguinal canal.

Nontesticular Masses

Hydrocele and Indirect Inguinal Hernia

Hydroceles can be differentiated from other testicular masses by transillumination of the fluid with a penlight. Patients with hydroceles also have a palpably normal spermatic cord and inguinal ring above the swollen area. In an upright position or during Valsalva maneuver, hernia and noncommunicating hydrocele enlarge. Scrotal ultrasonography may be helpful in making the diagnosis [1].

Hydroceles are caused by incomplete obliteration of the processus vaginalis allowing a collection of peritoneal fluid between the parietal and visceral layers of the tunica vaginalis surrounding the testicle. Communicating hydroceles have freely flowing fluid between the peritoneal cavity and the tunica vaginalis while noncommunicating hydroceles do not. Hydroceles occur more frequently on the right and are often bilateral [1, 2].

Pediatric hernias are present in 0.1–0.2% of live births. Risk factors include prematurity and low birth weight. Sudden presentation in an adult of a noncommunicating hydrocele may be secondary to torsion, neoplasm, injury, or infection. Adult hydroceles require no treatment unless they are uncomfortable [1].

Inguinal hernia and communicating hydrocele are indications for surgery in children. Noncommunicating hydroceles often spontaneously close by 1–2 years of age and should not be repaired until that time. Repair by high ligation of the patent processus vaginalis is the same for both hydrocele and inguinal hernia.

Varicocele

A varicocele is a dilation of the venous pampiniform plexus of the spermatic cord, which coalesces into a single testicular vein. The majority are left sided resulting from higher pressures on the left compared to the right. Varicoceles are classically described as feeling like a bag of worms; this feeling increases with Valsalva maneuvers. Varicoceles occur in 15% of males and usually first appear in adolescence. There is conflicting evidence about the association between varicoceles and male infertility [1]. A meta-analysis of 12 randomized controlled trials found some increases in testicular volume and sperm concentration from surgical treatment of varicoceles in children and adolescents; however, long-term outcomes for paternity and fertility remain unknown [3]. Sudden adult left-sided varicocele may indicate renal tumor, and right-sided varicocele could indicate obstruction of the vena cava.

In adolescent boys, evaluation of testicular size is important to determine the need for surgical correction. Sonography, a comparative orchidometer, or punched-out elliptical rings can be used to determine size. A volume difference between the testicles of greater than 2 cm^3 is the minimal requirement for surgical repair (Figs. 1 and 2).

Spermatocele and Epididymal Cyst

A spermatocele or epididymal cyst presents as a painless mass superior and posterior to the testicle and is completely separate from the testicle (cysts of the rete testes, epididymis, or ductuli efferentes). Enlarged and symptomatic cysts should be removed.

Epididymitis

Epididymitis is the most common cause of scrotal pain in adults and is characterized by acute unilateral pain and swelling [1]. The pain usually begins at the epididymis and can spread to the

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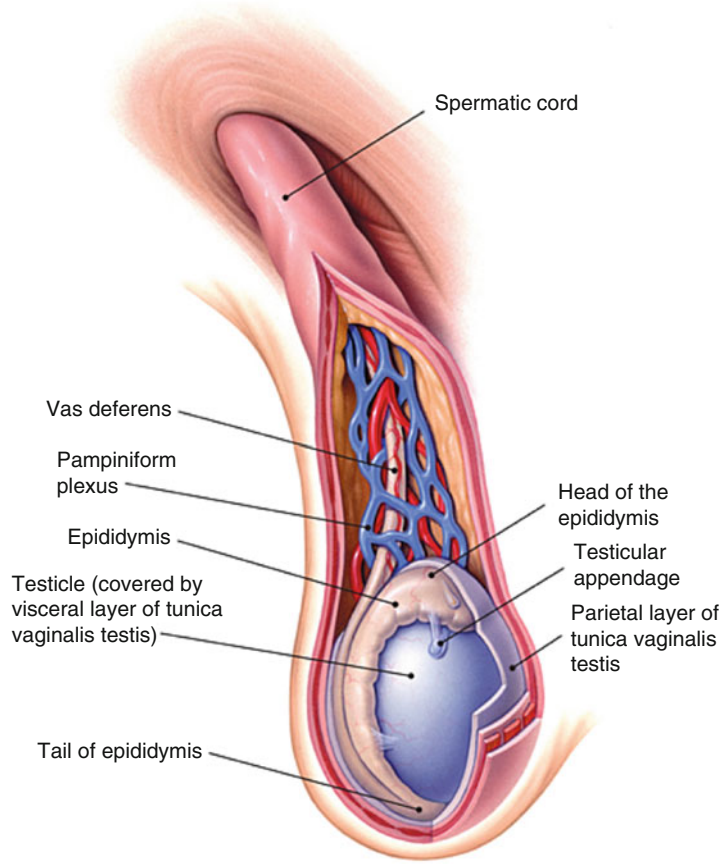


Fig. 1 Anatomy of scrotal contents

entire testicle (epididymo-orchitis). Other symptoms include fever, erythema of the scrotal skin, and dysuria. It is associated with a C-reactive protein level of more than 24 mg per L (228.6 nmol per L) (96% sensitive and 85% specific for epididymitis/orchitis) [4] and increased blood flow on ultrasonography. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most common organisms responsible for bacterial epididymitis in males younger than 35 years [5]. Guidelines recommend empiric ceftriaxone (Rocephin) and doxycycline for treatment of suspected epididymitis in males younger than 35 years [6]. Epididymitis may cause a painful swelling of the testicle and is a common cause of a painful testicle in postpubertal males. Presentation is usually of increasing testicular pain and discomfort and can be accompanied by urethral discharge. On exam, the epididymis is enlarged and may be indistinguishable from the testicle. The epididymis is tender and may be indurated [7].

Treatment should be directed at the most likely cause. For suspected UTI, levofloxacin (Levaquin) 500 mg orally twice daily for 10 days is usually adequate. In prepubertal boys, an evaluation of the GU system to include urinary system sonography and a voiding cystourethrogram should be considered.

Testicular Masses

Testicular Torsion

Testicular torsion or torsion of the testicular appendages presents as a painful testicle that is often enlarged or demonstrates a mass. These topics are covered in ▶ Chap. 104, "Surgery of the Male Genital Tract."

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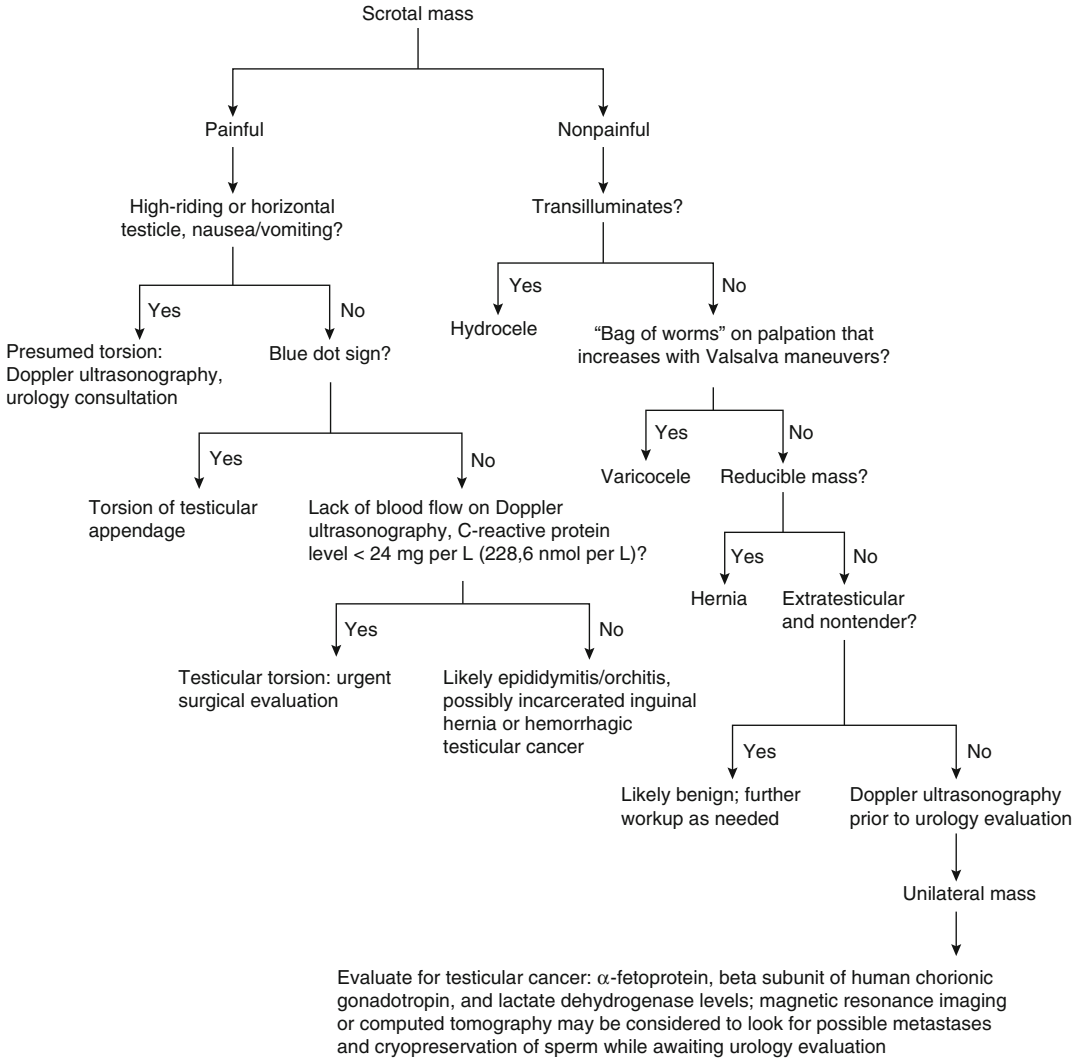


Fig. 2 Algorithm for evaluation of a scrotal mass

Acute Orchitis

Acute orchitis presents with sudden onset of testicular pain and high fever, usually with nausea and vomiting. On exam the testicle is tender, enlarged, and may be indurated. The most common causes are bacterial and viral infections. Mumps orchitis occurs in 20–35% of cases of mumps parotitis and presents 3–4 days after onset of parotid symptoms. Management of acute orchitis includes bed rest, scrotal support, ice, and analgesics. Antibiotics are important if a bacterial cause is suspected. Since only 15% of cases are bilateral, infertility is rare.

Testicular Cancer

Epidemiology and Risk Factors

Although only occurring in 6 out of 100,000 men annually in the United States, testicular cancer is the most common solid tumor among men between the ages of 20 and 34 years old and accounts for approximately 1% of all cancers in men [8, 11]. The most important risk factor for testicular cancer is cryptorchidism – 10% of cancer cases have a history of cryptorchidism. Cryptorchidism increases testicular cancer risk 3- to 17-fold. Early orchidopexy (before 1 year of

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age) reduces, but does not eliminate, this increased risk. Orchidopexy later in life is not as effective at reducing rates of cancer. Other risk factors include family history, infertility, tobacco use, white race, and a history of testicular cancer [9].

Screening

The US Preventive Services Task Force does not recommend screening for testicular cancer with either self- or physician examination [11].

Pathology

Germ cell tumors account for more than 90% of all testes tumors, the majority of which are classified as pure seminomas or nonseminomas. Most nonseminomatous germ cell tumors are composed of a combination of the following histological patterns: embryonal carcinoma, teratoma, teratocarcinoma, and choriocarcinoma [9].

The most common non-germ cell testicular tumors are Sertoli and Leydig cell tumors. The majority of these tumors are benign. Leydig cell tumors can present with sequelae of increased androgen production such as precocious puberty in boys and virilization in girls [9].

Diagnosis and Evaluation

Patients with testicular cancer are usually asymptomatic, but they may present with acute pain in the testicle or scrotum, dull ache in the scrotum or abdomen, scrotal heaviness, firmness of the testicle, infertility, intratesticular mass, or painless swelling/redness. Five percent of patients present with symptoms of metastasis to include gastrointestinal symptoms, gynecomastia, lumbar back pain, neck mass, and respiratory symptoms (e.g., cough, hemoptysis, dyspnea) [8].

All intratesticular masses should be considered a malignancy until proven otherwise. Patients with testicular masses should have a scrotal ultrasound to confirm the presence of a solid intratesticular mass and to evaluate the contralateral testicle. When cancer is a concern in a patient with a testicular mass, laboratory testing includes α-fetoprotein (AFP), beta subunit of human chorionic gonadotropin (β-HCG), and lactate dehydrogenase levels since >90% of patients with a nonseminomatous germ cell tumor have elevated levels of one or all of these [8]. Urgent referral to a urologist is indicated for patients with intratesticular masses, even though smaller masses are less likely to be cancerous. Patients with intratesticular masses should generally undergo radical orchiectomy through an inguinal approach; however, there is some evidence that more conservative testicular sparing surgery may be curative, though it is generally not considered first-line treatment at this time. For small tumors, active surveillance is a recommended option in compliant patients who are amenable to frequent follow-up and monitoring [10]. There is no role for needle biopsy. Once diagnosed with a germ cell tumor, patients should be staged with an abdominal computed tomography (CT) scan and chest radiographs.

Treatment

Clinical stage and histology determine appropriate therapy. Typical chemotherapy agents include bleomycin (Blenoxane), etoposide (VePesid), cisplatin (Platinol AQ), EP (etoposide, cisplatin), and VIP (etoposide, ifosfamide (Ifex), cisplatin).

Seminoma [8, 9]

- Stage I – active surveillance is preferred; however, single-agent carboplatin or radiotherapy is an alternative.
- Stage IIA is treated with radiation to the regional lymph nodes; however, chemotherapy with four cycles of etoposide (EP) or three cycles of bleomycin (BEP) is an alternative.
- Stage IIB is treated with chemotherapy with four cycles of EP or three cycles of BEP; however, radiotherapy of regional lymph nodes is an alternative.
- Stage IIC is treated with chemotherapy with four cycles of EP or three cycles of BEP.
- Stage III is treated with four cycles of EP or three cycles of BEP.

Nonseminoma [8, 9]

- Stage IA – active surveillance is preferred; however, retroperitoneal lymph node dissection (RPLND) is an alternative.

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- Stage IB – active surveillance is preferred; however, RPLND or one or two cycles of BEP are options.
- Stage IIA is treated with RPLND or chemotherapy with four cycles of EP or three cycles of BEP.
- Stage IIB is treated with chemotherapy with four cycles of EP or three cycles of BEP; RPLND can be considered in select cases.
- Stage IIC is treated with chemotherapy with four cycles of EP or three cycles of BEP.
- Stage IIIA is treated with chemotherapy with four cycles of EP or three cycles of BEP.
- Stage IIIB is treated with chemotherapy with four cycles of BEP.
- Stage IIIC is treated with chemotherapy with four cycles of BEP or VIP in select patients.

Complications of Treatment

Complications can result from chemotherapy, radiation, surgery, or the disease process. Chemotherapy-specific complications include azoospermia, lung disease (with bleomycin use), neuropathy (with etoposide use), renal or otologic injury (with cisplatin use), increased risk of cardiovascular disease, infertility, recurrence, cardiac mortality after radiation, and second malignancy (e.g., leukemia) after radiation or chemotherapy [8, 9].

Urothelial Tumors (Bladder Cancer)

Epidemiology and Risk Factors

Bladder cancer is the sixth most prevalent malignancy in the United States, accounting for approximately 7% of cancers in men and 3% of cancers in women. Annually in the United States, about 62,000 men and 19,000 women are diagnosed with this disease, while 18,000 die from it annually. The incidence of bladder cancer increases with age in men and women. Ninety percent of cases occur in those over 55 years of age [12].

The most significant risk factor for bladder cancer is cigarette smoking, which accounts for approximately 50% of all bladder cancer cases. It increases bladder cancer risk by four- to sevenfold. Other established risk factors include male sex, older age, white race, occupational exposure to certain chemicals, pelvic radiation, use of medications such as cyclophosphamide, chronic bladder infections/irritation, and personal or family history of bladder cancer. Bladder cancers may be associated with diabetes mellitus, obesity, and HPV [12]. The diabetes medication pioglitazone (Actos) has been independently associated with a slightly increased risk of bladder cancer.

Pathology

About 90% of bladder cancers diagnosed in the United States are urothelial, formerly known as transitional cell, carcinomas.

Squamous cell carcinoma accounts for about 7% of bladder cancers in the United States. Adenocarcinoma of the bladder is rare, accounting for fewer than 2% of all bladder cancers. Adenocarcinomas of the bladder are more common in patients with a urachal remnant or in patients who were born with bladder exstrophy [12]. In areas of the world with endemic schistosomiasis, squamous cell adenocarcinoma actually accounts for up to 81% of bladder cancers.

Location

About 96% of urothelial malignancies occur in the bladder. Upper tract (ureters and collecting system) tumors occur in 2–3% of patients with bladder tumors, while 30–75% of patients with upper tract tumors have associated bladder tumors. Bilateral involvement occurs in 2–5% of all patients with upper tract transitional cell carcinomas.

Screening

Screening for bladder cancer is not recommended [13].

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Diagnosis and Staging

Painless hematuria is the most common presenting sign or symptom of bladder cancer. The incidence of bladder cancer in a patient with gross hematuria is 20% and with microscopic hematuria is 2% [12]. Other less common signs include urinary frequency, irritability, and dysuria. Although the vast majority of bladder cancers are associated with microscopic hematuria, the hematuria frequently is intermittent, and a negative urinalysis does not exclude bladder cancer. All patients with hematuria should be evaluated with a urine cytology, cystoscopy, intravenous, CT, or MRI. Those with gross hematuria should be further evaluated with a renal ultrasound or CT.

Urine cytology has a high sensitivity (>90%) for the detection of high-grade urothelial cancers; however, renal calculi and urinary tract infections can lead to false-positive results [12]. Urine cytology is a helpful adjunct for surveillance in those with known urothelial carcinoma and the evaluation of patients at high risk of urothelial tumors due to its positive predictive value.

Cystoscopy is the primary diagnostic tool for bladder cancer. Once a tumor is identified, transurethral resection is performed to confirm the diagnosis and to determine the tumor stage. The primary goal of staging is to determine if the cancer is superficial or invasive. TNM staging of bladder cancer is very complex with 14 types of T, 5 types of N, and 4 types of M. Since transurethral resection can frequently understage patients, frequently patients with high-grade Tl disease are treated as if they had muscle-invasive disease [12, 14].

CT examination of the abdomen and pelvis is obtained in patients with muscle-invasive bladder cancer (T2 or higher) and/or high-grade disease to evaluate the perivesical soft tissue, pelvic and retroperitoneal lymph nodes, as well as the liver and adrenal glands. CT scans are relatively unreliable in determining depth of tumor invasion and may fail to detect lymph node metastasis in up to 40% of patients with them [12].

CT, MRI, or intravenous urograms or retrograde ureteropyelograms should be obtained in all patients with bladder cancer to exclude the presence of an upper tract transitional cell carcinoma.

Treatment

Treatment of bladder cancer is different for each stage. Low-grade Ta through high-grade T1 cancer is generally treated with transurethral resection and intravesical *Bacillus Calmette-Guerin* (BCG) or mitomycin. T2a through T3b are treated with radical cystectomy and bilateral pelvic lymphadenectomy followed by either chemotherapy or adjuvant chemotherapy. T4a through metastatic disease is treated with chemotherapy alone or in combination with radiation therapy [12].

Urinary reconstruction following cystectomy is an important component in the management of patients with invasive bladder cancer. Various modalities to restore a semblance of normal urinary function using cutaneous diversions (both catheterizable and noncatheterizable) are in use currently. Other options in which a reservoir is connected directly to the native urethra lessen the impact of cystectomy on quality of life. These diversions can be performed successfully in men and women.

Additionally, radical cystectomy can preserve the neurovascular bundles in men and the vagina in women. Thus, normal urinary and sexual function can be retained despite curative therapy for invasive bladder cancer. Anastomotic strictures can be common, so patients must be followed closely for the development of hydronephrosis and deterioration of renal function.

Urolithiasis

Urolithiasis is common. Family physicians must distinguish it from other causes of abdominal and flank pain. Urolithiasis causes pain when a stone partially or completely obstructs the collecting system or ureter while it migrates. Distal ureteral stones may be associated with dysuria, frequency, and penile or labial pain, while stones in the renal

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collecting system may be painless. Classically, the patient presents with severe, colicky, unilateral flank, or lower abdominal pain. The pain may radiate to the groin, scrotum, or labia and be associated with nausea and vomiting, dysuria, gross hematuria, urinary frequency, or fever. Fever is present when associated with UTI. Conditions that may be similar to or mimic renal colic include pyelonephritis, urethritis, prostatitis, vaginitis, pelvic inflammatory disease, pelvic pain syndrome, gallbladder disease, various gastrointestinal diseases, dissecting abdominal aortic aneurysm, ovarian or testicular pathology, ectopic pregnancy, and ureteral tumors [15].

Epidemiology

Lifetime risk of developing urolithiasis is 10–15% with higher prevalence in the southeastern United States. It is two to three times more common in males than females and affects Caucasians more than Asians and Blacks. Incidence peaks between 30 and 50 years old, and recurrence rates are as high as 40–75% over 25 years. Frequency of different stone types varies greatly with the population studied. In the United States, calcium stones are by far the most common, with calcium oxalate stones accounting for 56–61% and calcium phosphate stones accounting for 8–18%. Less common (in descending order) are uric acid, magnesium ammonium phosphate (struvite), and cystine stones. Children have more struvite than uric acid stones [15, 16]. Chronic medical conditions can increase the risk of developing certain times of stones. For example, patients with Crohn's disease and ulcerative colitis, pancreatic insufficiency, and a history of bariatric surgery are more likely to develop calcium oxalate stones [19].

Etiology

In modern times, obesity and diabetes are common causes of urolithiasis. Other diseases such as primary hyperparathyroidism, type 1 renal tubular acidosis (RTA), Crohn's disease, primary hyperoxaluria, and cystinuria are associated with recurrent urolithiasis but account for less than 5% of patients with stone disease. An etiology for urolithiasis can be determined 97% of the time after an appropriate workup. Etiologies of urolithiasis are listed in Table 1. Metabolic abnormalities account for the majority of disease. Sixty percent of calcium stone disease is caused by idiopathic hypercalciuria. Hyperuricosuria, followed by hypocitraturia and hyperoxaluria, is the next most common metabolic abnormality causing disease. Medications that may also play a role in stone disease are listed in the table. High dietary fructose intake is also associated with urolithiasis.

Table 1 Causes of urolithiasis [15–18]

Obesity	Hypomagnesuria
Diabetes	Hyperoxaluria
Hypercalciuria	Increased dietary fructose intake
Idiopathic (absorptive types I and II)	Medications and supplements
Renal	Allopurinol
Unclassified	Antibiotics (sulfonamides, ampicillin, amoxicillin, ceftriaxone (Rocephin), quinolones, furans, pyridines)
Primary hyperparathyroidism	Carbonic anhydrase inhibitors (acetazolamide, topiramate (Topamax))
Hyperuricosuria	Ephedra alkaloids
Cystinuria	HAART (highly active antiretroviral therapy)
Gouty crystal deposits	Laxatives
Stones secondary to urinary infection	Potassium channel blockers (amiodarone, sotalol)
Renal tubular acidosis type 1	Potassium-sparing diuretics (triamterene)
Hypocitraturia	Sulfonylureas

Evaluation

Family physicians must take a thorough history including presenting symptoms, medical history (e.g., gout, bowel disease), medications and supplements, diet, and family history of stone disease

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or related illnesses. Physical exam of the flank, abdomen, groin, and genitals is most useful, and physicians should use physical exam to rule out other possible diagnoses. Urinalysis with urinary pH and microscopic examination for red blood cells, white blood cells, and crystals should be performed [19]. Hematuria is 67% sensitive and 58% specific for urolithiasis. Presence of white blood cells or crystals can indicate concomitant infection or hyperuricemia. Urine culture should also be obtained to evaluate for infection.

Diagnostic imaging is the next step in evaluation. A prudent and safe first step is to perform an ultrasound of the kidney and collecting system. Patients with a positive ultrasound need not have a CT scan with its attendant radiation. Those with negative ultrasound should progress to unenhanced helical CT – with reported sensitivity of 95–100% and specificity of 94–96% in diagnosing urolithiasis. Advantages of this imaging technique include avoidance of intravenous contrast, short duration (approximately 5 min to perform), ability to visualize all stone types, localization of stone within the ureter, identification of secondary signs of obstruction when a stone has recently passed, and ability to diagnose other abdominal and pelvic pathology when urolithiasis is not present. Additionally, the use of CT scans allows for better quality imaging in obese patients and may be more available compared to ultrasound [19]. Using Hounsfield density helical CT allows one to differentiate uric acid, cystine, and calcium-containing stones from one another and to subtype calcium stones.

Plain radiography is only useful if other conditions are suspected as the cause of pain due to low sensitivity and specificity. Only calcium-containing stones are radiopaque, but this fact is complicated by the fact that calcifications seen on plain radiograph may or may not be associated with the urinary system.

Intravenous urography (IVU) is a less desirable option than ultrasound or CT scan. IVU can usually detect ureteral obstruction based on dilation of the collecting system or ureter, a delayed nephrogram, or delayed excretion of contrast. IVU is limited in that signs of obstruction may not appear acutely, radiolucent stones cannot be visualized, and many other causes of abdominal pain cannot be evaluated. Intravenous contrast is necessary when performing an IVU and can cause postcontrast nephropathy and numerous systemic reactions.

Approach to Management

Urolithiasis complicated by an infected stone and/or urosepsis is an emergency. Emergent urological consultation for either immediate drainage by percutaneous nephrostomy or retrograde ureteral stent insertion is necessary since these patients have a high mortality. Other indications for urgent urological consultation are anuria, bilateral obstruction, obstruction of a sole functioning kidney, hydronephrosis, concomitant pregnancy, and renal failure. Those patients with refractory pain as well as those with potential comorbidities such as arteriopathy or are older than age 60 should also be referred.

In the absence of these conditions, stone size and location determines the next step. Ureteral stones with a width 4 mm or less will spontaneously pass in 80% of patients, while rates fall to 35% at 5 mm and 25% at 7 mm. Patients with stones <5 mm in width should be provided adequate analgesia. Maintaining urine volumes greater than 2.5 L a day is essential [18]. Patients should be instructed to strain their urine and bring in any stones for analysis and should follow up immediately for symptoms of urosepsis. Stone passage may be monitored with plain radiographs and a urological referral made if stones are not passed within 4–6 weeks. At this time, patients with persistent stones are often offered either ureteroscopy to remove stones or extracorporeal shock wave lithotripsy (ESWL) to remove stones.

Antispasmodics

Calcium channel blockers and alpha blockers should be first-line therapy for urolithiasis. These medications not only reduce the pain from renal colic by reducing smooth muscle spasm in

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the ureter, they also reduce the time of passage of stones <10 mm by 5–7 days. Alpha blockers should be prescribed as follows: doxazosin (Cardura) 4 mg orally per day or tamsulosin (Flomax) 0.4 mg orally per day. If calcium channel blockers are chosen, then nifedipine (Procardia) 30 mg orally per day should be used.

Analgesia

Adequate pain control often requires a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics. As a note of caution, patients with reduced renal function should be prescribed NSAIDs only after the risks of further kidney damage are considered and discussed with patients [14]. Any NSAID is acceptable to treat urolithiasis for a short period. Long-term treatment entails more risk, and physicians should consider naproxen (Naprosyn) 500 mg twice daily due to its lower risk of thrombosis. NSAIDs must be held for 3 days prior to ESWL because of antiplatelet effects and risk of bleeding, and aspirin should be held for 7 days prior to ESWL.

Narcotics used for pain control include hydrocodone 5 or 10 mg with acetaminophen 325 mg (Vicodin 10/325) orally every 4–6 h as needed, oxycodone 5 mg with acetaminophen 325 mg (Percocet 5/325) orally every 4–6 h as needed, and codeine 30 mg with acetaminophen 300 mg (Tylenol with codeine No. 3) orally every 4–6 h as needed. An antiemetic such as promethazine (Phenergan) 25 mg orally or ondansetron (Zofran) every 6 h may also be helpful.

Surgical Management

Stone location and size are the primary determinants when choosing which procedure to use for stone removal. ESWL is minimally invasive and is effective for calculi <1 cm in the ureter and <2 cm in the kidney. Basket retrieval through a cystoscope or ureteroscope is indicated for lower ureteral stones not amenable to ESWL [14]. Larger stones may be treated with percutaneous nephrolithotomy alone or in combination with ESWL [19]. All of these procedures carry minimal surgical risk, and analgesia with either NSAIDs or narcotics is appropriate post procedure. Staghorn renal calculi should always be treated because of their high complication rates. Asymptomatic renal stones do not require treatment but become symptomatic in 50% of patients over 5 years.

Metabolic Evaluation

All patients with stone disease should have a basic workup to identify underlying metabolic or environmental factors causing stone formation. A more in-depth workup should be completed in patients with recurrent urolithiasis.

Minimal evaluation should include urinalysis (including pH) with urine culture, stone analysis when possible, and serum calcium, phosphorus, uric acid, creatinine, and electrolytes. Table 2 shows stone analysis compared with diagnosis.

If no stone is available to analyze, a 24-h urine collection for a stone risk profile while the patient is on their customary diet should be performed. Expert consensus panels recommend this, but there are no trials to determine its effectiveness. The stone risk profile includes urine calcium, oxalate, uric acid, citrate, pH, total volume, sodium, sulfate, phosphorus, magnesium, and urinary saturation of calcium oxalate, brushite, monosodium urate, and uric acid. Once this is completed, dietary modifications to reduce abnormalities in the stone risk profile should be initiated with a

Table 2 Stone composition and diagnosis [14, 15, 17, 18]

Stone composition	Diagnosis
Cystine	Cystinuria
Struvite	Stone due to infection
Uric acid	Hyperuricosuria
	Low pH (gout, diarrhea)
Calcium phosphate	Primary hyperparathyroidism (increased calcium, low phosphorus)
	Renal tubular acidosis (hypokalemia and metabolic acidosis)
	Sodium alkali therapy

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Table 3 Dietary changes in response to stone risk profile [14, 17, 18]

Urinary oxalate >45 mg per day	Avoid tea, spinach, dark roughage, chocolate, and nuts
	Take no more than 500 mg of vitamin C daily
Urinary calcium >250 mg per day	Moderate calcium restriction
Uric acid level > 700 mg per day	Restrict protein
Sulfate level > 30 mmol per day	Restrict protein
Low urine pH	Increase intake of potassium-rich citrus fruits
Low urine citrate	Increase intake of potassium-rich citrus fruits
Low urine pH	Increase intake of potassium-rich citrus fruits

concomitant increase in fluid intake to maintain a urine volume of >2.5 L a day. These dietary changes include a sodium restriction of 200 mEq daily for all patients. Other dietary changes are listed in Table 3.

After 1 week, the stone risk profile is repeated and the two completed stone profiles compared. If abnormalities are corrected by dietary modification and increased hydration, then environmental changes are recommended. If abnormalities persist, then appropriate treatment is initiated.

Treatment

In spite of poor evidence, all patients should be told to drink a minimum of 2 L of fluid a day, eat a diet high in potassium-rich citrus fruits, and restrict intake of protein, oxalate, and sodium.

Hyperoxaluria

Non-dietary hyperoxaluria (>45 mg per day) is seen with inflammatory bowel disease, small bowel resection, and intestinal malabsorption of fat. Dietary restriction of oxalate is the main form of treatment. Patients should be counseled to limit intake of oxalate-rich foods and maintain normal calcium consumption [18].

Hypercalciuria

Patients with hypercalciuria (>250 mg per day) associated with hypercalcemia should be evaluated for primary hyperparathyroidism. When hypercalciuria is seen with excess urinary sodium, dietary restriction of sodium 100 mEq per day is recommended. Absorptive hypercalciuria and renal hypercalciuria are the probable causes when the abovementioned conditions are not present. Both can be treated with thiazides such as hydrochlorothiazide 25 mg daily with potassium citrate 20 mEq twice daily. Doses of potassium citrate may be adjusted based on follow-up serum potassium and urinary citrate levels.

Hypocitraturia

High intake of animal proteins is the usual cause of mild to moderate hypocitraturia (100–320 mg per day). It is best treated with potassium citrate 20 mEq twice daily and restriction of animal protein. Chronic diarrhea and renal tubular acidosis (RTA) cause severe hypocitraturia (<100 mg per day). When diarrhea is present, treatment is directed at the diarrhea. Potassium citrate 20–40 mEq twice daily may be given.

Hyperuricosuria

Excess intake of purines causes hyperuricosuria (>700 mg per day) without elevated serum uric acid. Allopurinol (Zyloprim) 300 mg daily and potassium citrate can prevent further stones in combination with dietary restrictions. When hyperuricosuria is found in combination with elevated uric acid and low urinary pH, gout is present. Allopurinol 300 mg daily, along with potassium citrate if urinary pH is low, is recommended. Limitation of non-dairy animal protein may help reduce stone recurrence as well [18].

Prevention of Urolithiasis

There is a poor evidence base for practice patterns to prevent urolithiasis. Regardless, consensus guidelines recommend hydration, dietary therapy, use of potassium citrate, and thiazide diuretics to prevent recurrence in spite of

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potential adverse effects [15]. Medications used for stone prevention may cause adverse side effects, so periodic monitoring of blood work is recommended [18].

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Part XXI

The Female Reproductive System and Women's Health

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Family Planning, Birth Control, and Contraception

106

Melanie Menning and Peter Schindler

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Before discussing family planning, birth control, and contraception, it is crucial to define the terms. Family planning/birth control are contraceptive methods, treatment of infertility, procedures, devices, and behaviors that allow people to obtain their desired number of children and determine the spacing of pregnancies. Contraception is a

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subset of family planning/birth control, defined as the intentional use of artificial methods or other practices to prevent pregnancy. The primary forms of contraception are a barrier method, hormonal, nonhormonal IUD, and sterilization.

Contraceptive Use in the United States

As of 2017, there are 72.2 million US women of reproductive age, defined as women aged 15–49, who are using contraception [1]. The most common methods in decreasing order are female sterilization, oral contraception pills, long-acting reversible contraceptives (LARCs), and male condoms [1]. Despite the popularity of modern contraceptive methods, 10% of women of reproductive age are not currently using a contraceptive method to prevent unwanted pregnancy [1]. There are a variety of reasons for not using a contraceptive/family planning method. Often religion is cited as the principal reason for not using a contraceptive method. Research suggests that many women, regardless of religious affiliation, will use a contraceptive method other than natural family planning in their lifetime [2]. The usage rates are significant because, in general, couples who do not use any method of contraception or birth control have approximately an 85% chance of becoming pregnant over a year [3]. Putting this in perspective, in the United States, the average desired family size is two children [4]. To be able to keep a family size at two or less, a woman must use contraception or birth control/family planning for at least three decades [4].

Women aged 15–19 (18%) have the highest risk of becoming pregnant. The lowest risk group is women aged 40–44 (9%) [2]. Contraceptive use does vary by race and ethnicity. Of women that are of reproductive age, 83% of black women at risk of unintended pregnancy are currently using a contraceptive method. Roughly 90–91% of white, Hispanic, and Asian women are presently using a reliable form of contraception [2]. Another vital aspect to take into consideration is socioeconomic status. About 8% of women living greater than 300% below the poverty line are not currently using a contraceptive method [2]. At a global level, preventing unwanted pregnancies has been a UN Millennium development goal for quite some time. Understanding the basic uptake of contraceptive methods in the USA is essential when considering who is at the greatest risk of unintended pregnancy. In general, understanding local and regional beliefs surrounding contraception and family planning/birth control can aid in providing the most pertinent medical advice and help in dispelling myths and misperceptions of contraceptive methods.

What Are the Most Popular Contraceptive Methods?

In general, the uptake of contraceptive methods is highest among older women and non-Hispanic white women when compared with younger women and non-Hispanic black women [1]. Most (72%) women who use contraception are currently using reversible forms of contraception. Most forms are primarily hormonal methods, such as the pill, implant, patch injectables, vaginal ring, IUDs, and condoms [5]. A minority of women and their partners (28%) rely on permanent methods such as sterilization [5]. Within sterilization, women are more likely than men to have a sterilization procedure performed despite the more invasive nature of the procedure when performed on women. Female sterilization usage is not uniform among subgroups of women. Sterilization is most prevalent among: African Americans and Hispanics, women over the age of 35, women who have birthed more than two children, women living in poverty, women living in rural areas, women who have not attended education at the university level, and women with no health insurance [2].

There are some commonalities among women who most commonly use an IUD or implant. This particular subset of women tends to be 25–34-year-old, born outside of the USA, currently reside in the western region of the USA, and self-described as "other" to a religious group [6]. Women are more likely to choose a long-acting reversible contraceptive method (LARC) if they have had a child or have used a non-LARC hormonal method in the past [6].

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Another extremely common contraceptive method is the male condom. Almost six million women list the male condom as the only form of contraception they use. There are known sociodemographic characteristics of individuals who are more likely to use the male condom: Individuals who are between 15 and 19 years of age, uninsured persons, those educated at the university level, and those who have never had a child or are expecting at least one (more) child [5]. While condoms alone are not an effective form of contraception, dual method use (barrier method combined with another form of contraception) offers protection against both pregnancy and STIs. However, only about 8% of women of reproductive age concurrently use multiple contraceptive methods [7].

Teen Contraceptive Use

Preventing unintended pregnancy among teenagers is a way to help avoid the intergenerational perpetuation of poverty [8]. Eighty-two percent of women between the ages of 15 and 19 are using a contraceptive method. Of the 82% of women, 59% were using a highly effective method such as hormonal contraception or IUDs [9]. More specifically, the most common forms of contraception among teenagers are the male condom, combined contraceptive pills, withdrawal technique, injectable hormonal contraception, patch or ring, and the IUD [10, 11]. Most teenagers tend to use a form of contraception when initiating sexual intercourse for the first time [9]. Using some form of contraceptive is especially important as the likelihood of giving birth before age 20 was twice as high for teenage women who had not used a contraceptive method at the time, they initiated sexual intercourse when compared to women who had [9]. Concerning dual methods, the most recent data available show about one fifth of sexually active females aged 15–19 and one-third males the same age report having used both the male condom and a hormonal method the last time they had sex [9].

Provider Tools

CDC- US MEC

There are a wide variety of provider resources available. The most comprehensive tool available is the CDC US Medical Eligibility Criteria (US MEC) for contraceptive use, 2016. The resource provides general recommendations regarding particular contraceptive methods for men and women. The resource is comprehensive and contains recommendations for specific health conditions such as multiple sclerosis and also discusses subpopulations of people such as postpartum or HIV positive individuals on antiretroviral therapy.

WHO Medical Eligibility Criteria for Contraceptive Use

The WHO Medical Eligibility criteria for contraceptive use is another comprehensive guide intended to improve the quality of care in family planning. The document can be found on the WHO website and is downloadable. There is also a free mobile app available. The WHO medical eligibility guide tends to have much of the same types of information as the CDC US medical eligibility guide with additional provider tools such as the "medical eligibility wheel for contraceptive use."

The Family Planning National Training Center (FPNTC)

The goal of the FPNTC is to ensure those who work in the area of family planning have the skills and knowledge necessary to provide comprehensive family planning care. The FPNTC collaborates closely with the National Clinical Training Center for Family Planning (CTCFP) at the University of Missouri-Kansas City, which delivers clinical skills training and resources to health care providers in the Tile X and related public health communities' mainly Planning National Training Center (FPNTC)

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Association of State and Territorial Health Officials (ASTHO)1

Per the organization's website, ASTHO is a national not-for-profit organization representing public health agencies across the USA and US territories. The organization exists mainly to track, evaluate, and advise members of public health about health policy. The organization specifically provides guidance and strategies for implementing LARCs at the provider level.

Non-English Resources for Patients

The US National Library of Medicine (MedlinePlus) contains many family planning/contraceptive handouts in multiple languages such as Burmese, Chinese: Mandarin and Cantonese, Dari, Farsi, Hindi, Hmong, Karen, Kinyarwanda, Nepali, Pashto, Portuguese, Russian, Spanish, Tagalong, and Vietnamese. Topics range from Vasectomy care to emergency contraceptive counseling. For those who care for diverse populations with family planning needs, this is considered an essential resource.

Long-Acting Reversible Contraceptives (LARC)

Long-acting reversible contraceptives (LARC) are a variety of contraceptive methods that are effective at preventing pregnancy for a prolonged period without requiring any user maintenance. Types of LARCs include subdermal contraceptive implants, IUDs, and injections. LARCs do not rely on patient compliance; therefore, their typical and actual failure rates are identical (Less than 1%). In general, LARCs have higher efficacy, higher continuation rates, and higher satisfaction rates compared with short-acting contraceptives among adolescents and adults who choose to use them [12–14].

Intrauterine Device (IUD)

Mechanism of action: The IUD is a T-shaped device that is inserted into the uterus. Its main mechanisms of action are to (1) irritate the uterine lining, (2) impairs sperm motility, (3) interfere with fertilization, and (4) inhibit implantation. There are two main types of IUDs available on the US market, progesterone containing (hormone) IUDs and a copper-containing IUD (non-hormonal). Progesterone containing IUDs release low levels of progesterone, which results in thickened cervical mucus, further inhibiting sperm motility. Also, the progestins themselves may impair fertilization. Concerning copper-containing IUDs, the copper ion itself is toxic to human spermatozoa and human ova. The copper IUD also enhances inflammatory responses, which are harmful to spermatocytes and oocytes.

One example of a hormonal IUD is the Levorgestril (LNG) containing Mirena IUD. Levonorgestrel is a potent progestin. It applies a significant effect on human cervical mucus, thickening enough for the mucus to act as a spermicidal barrier. Thick cervical mucus directly inhibits sperm capacitation, which effectively prevents conception. The levonorgestrel also causes atrophy of the endometrium. A sequela of the atrophic endometrium is that leads to a dramatic reduction of menstrual flow.

Availability: There are Five IUDs available in the United States [15]. The copper-containing IUD and four levonorgestrel-releasing IUDs. The LNG containing IUDs range from a total of 13.5 mg to 52 mg levonorgestrel.

Effectiveness: IUDs are incredibly effective; less than 1% of women become pregnant in the first year of having an IUD [3]. IUDs can be used by women of all ages, including adolescents, and by parous and nulliparous women. One crucial educational point for patients is that IUDs do not protect against sexually transmitted infections (STI). IUDs, combined with a barrier method, are an effective combination for preventing pregnancy and STIs.

Contraindications: Pregnancy, puerperal sepsis, immediate placement after septic abortion, distorted uterine cavity, cervical or endometrial cancer (awaiting treatment), gestational trophoblastic disease, breast cancer (progestin IUD only), AIDS not on antiretroviral therapy, pelvic tuberculosis, and unexplained vaginal bleeding

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Subdermal Contraceptive Implant

Mechanism of action: The subdermal contraceptive implants are typically a small single etonogestrel-containing rod inserted in the medial aspect of the arm. The implant's main mechanism of action is to inhibit ovulation. A secondary mechanism is an increase in cervical mucus viscosity, which inhibits sperm penetration.

Availability: There is one implant (Nexplanon) currently available in the USA.

Effectiveness: The subdermal implant is highly effective. In some cases, the Nexplanon is more effective than sterilization [12]. Less than 1% of women in the first year of use will become pregnant [3]. Since it is considered a LARC method, the typical and actual use rate is identical. Women of all ages can use the implant. One crucial educational point for patients is that subdermal implants do not protect against STIs. Implants combined with a barrier method are an effective combo for preventing pregnancy and STIs.

Contraindications

Relatively few. There are a few contraindications, such as severe rheumatologic conditions and current pregnancy. Consult provider resources for more in-depth information.

Other Considerations

If a woman desires the implant and it has been greater than 5 days since the initiation of her menstrual period, she must use a backup form of contraception for 7 days or abstain from sexual intercourse for 7 days [16]. After 7 days, if a pregnancy test is negative, then the implant may be placed. If it has less than 5 days since the initiation of the menstrual period, then no additional contraceptive protection is needed.

Injectables

Mechanism of action: Slow-release, medroxyprogesterone acetate (DMPA). One slow-release, 150 mg IM dose of DMPA, is given every 3 months. Contraceptive mechanisms of action for DMPA include ovulation suppression, thickening of the cervical mucus that blocks sperm motility, and endometrial changes that impede/prevent implantation [17].

Availability: One slow-release, 150 mg IM dose of DMPA given every 3 months. DMPA is also available in a micronized formulation for subcutaneous administration every 12 weeks. The subcutaneous preparation delivers a 30% lower total dose (104 mg) than the IM preparation but may suppress ovulation for at least 13 weeks, without being affected by body mass [18].

Effectiveness: DMPA is highly effective and generally well-tolerated contraceptives. For DMPA, cumulative pregnancy rates of 0.1–0.7% have been reported at 1 year [19], 0.4% at 2 years [19].

Other considerations: Bleeding pattern changes occur in between 20% and 40% of DMPA users [20] Approximately 50% of women using DMPA discontinue use by 1 year, primarily because of altered bleeding patterns [20]. Amenorrhea is 21% more likely to occur in women using DPMA [21]. Weight gain of up to 2–3 kg over 1 year has been reported with the use of these contraceptives in clinical trials [22]. Progestogen-only injectable contraceptives are associated with a delay of up to 1 year in the return to fertility after discontinuing use [23].

Data associating a reduction in bone mineral density (BMD) with progestogen-only injectable contraceptives are equivocal. Progestogen-only injectable contraceptives are associated with reduced BMD, but since the "fracture threshold" is not breached, an increased risk for fracture has yet to be demonstrated [24]. BMD normalizes after study drug discontinuation, although a concern in adolescents is that peak bone mass is never reached.

There is a possible etiological association between highly effective contraceptives such as DMPA and the risk of acquiring sexually transmitted infections, including HIV. DMPA does not appear to increase HIV risk among women in the general population, although further investigation is needed to verify this finding [25, 26]. Findings from a recent randomized study suggest an association between exposure to DMPA and the risk of

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HIV disease progression, which also urgently requires additional research [26].

Emergency Contraception

Mechanism of action: Emergency contraception is a way to prevent pregnancy after unprotected sex or contraceptive failure; it does not affect an established pregnancy [27]. The majority of dedicated emergency contraceptive products currently on the market are effective when taken within 72 h of unprotected sex (although they are decreasingly effective for up to 5 days after unprotected sex). Nonhormonal copper IUDs inserted up to 5 days after unprotected intercourse can also act as emergency contraception [27].

Availability: There are several products available in the USA, levonorgestrel and ulipristal acetate.

Effectiveness: Levonorgestrel must be taken within 72 h, and ulipristal acetate must be taken within 120 h. The effectiveness of the regimens varies among the method used. Levonorgestrel, for example, about 13 out of 100 women will still become pregnant after taking the pills [3]. On the other hand, ulipristal acetate, about six or out of every 100 women, may become pregnant after taking the pills [3]. The copper IUD is the most effective emergency contraceptive method. One out of 1000 women who use a copper IUD may become pregnant [3].

Combined Hormonal Contraceptives

Mechanism of action: Combined hormonal contraceptives (CHCs) include low-dose estrogen combined oral contraceptives (COCs), the combined hormonal patch, and the combined vaginal ring. The mechanism of action for the combined hormonal contraceptives is generally: ovulation suppression via estrogen and cervical mucus thickening, and endometrial thinning via progestin.

Other considerations: CHCs do not protect against sexually transmitted infections. Certain medications may affect the efficacy of combined hormonal contraceptives. Medications such as rifampin, anticonvulsants, HIV medications, and supplements can lower the efficacy of CHCs.

Vaginal ring: There are two vaginal rings available in the USA currently. The etonogestrel and ethynyl estradiol ring and the segesterone and ethynyl estradiol ring. The rings are very similar in size flexibility and shape but vary in the number of hormones and duration of use. The etonogestrel and ethynyl estradiol ring is a flexible ring that is inserted into the vagina and kept in place for 21 days. Then removed for 7 days for a withdrawal bleed. A new ring is inserted every month. The segesterone and ethynyl estradiol is a ring that is kept in place for 21 days then removed for 7 days. The main difference between the etonogestrel and segesterone ring is that the segesterone ring is not discarded after 21 days. A single Segerterone ring has been approved for 1 year. The contraceptive mechanism of action of the vaginal ring is primarily ovulation suppression [28]. Secondary mechanisms of action are likely cervical mucus thickening and endometrial thinning [28].

Effectiveness: The vaginal ring is not as effective as IUDs and the implant. Failure rates are overall low and very similar to the patch and COCs [29]. With typical use, about nine out of 100 women who use this method may become pregnant [3].

Hormonal patch: There are two formulations of the contraceptive patch available in the USA: The Ethinyl estradiol and norelgestromin patch: releases 25 mcg of EE and 150 norelgestromin and Ethinyl estradiol and levonorgestrel: releases 30 mcg of EE and 125 mcg of LNG per day.

The patch is changed once per week for 3 weeks (21 total days), followed by one patch-free week (7 days) [30, 31]. The patch is most effective if there is no more than a 7-day patch-free interval. The patch should always be changed/applied on the same day of the week (e.g., Sundays for Sunday start).

Effectiveness: The hormonal patch is a highly effective method; about one out of 100 women may become pregnant with perfect use. About nine out of 100 may become pregnant with typical use [3].

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Other considerations: There was a theoretical concern regarding body weight and hormonal patch effectiveness. Studies show that BMI does not seem to affect the efficacy of the hormonal patch [32].

Oral contraceptive pill: Mechanism of action is the suppression of ovulation by inhibition of gonadotropin-releasing hormone (GnRH), Luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and the mid-cycle LH surge. Both the progestin and estrogen hormones present in the combined oral contraceptives work together. Estrogen primarily suppresses FSH and subsequently prevents folliculogenesis. The progestin-related mechanisms are responsible for effects on the endometrium, such as thinning of the endometrial lining and thickening of the cervical mucus.

Effectiveness: With typical use, nine out of 100 women may become pregnant. With perfect use, the oral contraceptive pill is over 99% effective [3].

Other considerations: The most common adverse effect of combined oral contraceptive pills is breakthrough bleeding. Occasionally women may experience headaches, abdominal cramping, nausea, breast tenderness, and an increase in vaginal discharge or decreased libido. Most of the side effects can be relieved by switching to a different combined oral contraceptive formulation.

General Guidelines for Combined Hormonal Contraceptives

The combined hormonal contraceptives have some general principles when it comes to selecting candidates. Typically, the general guidelines hold for any form of contraception that uses estrogen and progestin as the two primary hormones. If a woman is over the age of 35 and smokes about a half a pack a day, has risk factors for arterial cardiovascular disease, hypertension (over 160 systolic, history of venous thromboembolism, not on anticoagulation), known ischemic heart disease, history of stroke, complicated valvular heart disease, current breast cancer, decompensated cirrhosis, hepatocellular adenoma or malignant hepatoma, migraine with aura, and diabetes of over 20-year duration or with complications with the disease such as nephropathy, retinopathy, or neuropathy other forms of contraception should be considered.

Barrier Methods

There are several barrier methods available; the male condom, female condom, diaphragm, cervical cap, spermicide sponge.

Mechanism of action: Prevent sperm from coming into contact with a woman's egg. Some barrier methods also protect against sexually transmitted infections.

Effectiveness: In general, barrier methods are not a very effective way of preventing pregnancy. About 20 women out of 100 may become pregnant when using barrier methods [3].

Condoms: Male and Female

Condoms create a physical barrier that can protect the user from STIs as well as prevent pregnancy. There are two main types of condoms available: male and female condoms. The male condom is a thin sheath worn over the penis during sexual intercourse. The female condom is a thin plastic pouch that lines the vagina. Latex and polyurethane condoms appear to provide the best protection against sexually transmitted infections. All condoms are single-use. 18 out of 100 women may become pregnant over the course of the year with the use of condoms as the primary contraceptive method [3].

Diaphragm and Cervical Cap

The diaphragm is a small, dome-shaped device made of silicone or latex that fits inside the vagina and covers the cervix. It typically is used with a spermicide. The diaphragm must remain in place for 6 h after sex, but not more than 24 h total. The cervical cap is a small plastic dome that fits tightly over the cervix and stays in place by suction. It must also be used with spermicide. Like the diaphragm, the cap must be left in place for at least

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6 h after intercourse. About 12% of nonpariuous women and 25% of multiparious women may become pregnant with the diarpham and cervical cap methods [3].

Spermicides

Mechanism of action: Spermicides are chemical compounds that kill sperm on contact. There is only one type of spermicide available in the USA, Nonoxynol-9 (N-9). There are a variety of formulations of N-9 such as a cream, foam, jelly, tablet, suppository, or film. The primary mechanism of action to prevent pregnancy is by stopping and killing sperm before they can reach an egg and fertilize it. Spermicides are typically used in combination with other barrier methods. If used, the spermicide should remain in the vagina at least 6 h after sex.

Effectiveness: Roughly 20–28 out of 100 women each year who use spermicides alone for birth control may become pregnant [3].

Permanent Contraceptive Methods: Tubal Sterilization and Vasectomy

Tubal sterilization and vasectomy for men are highly effective, safe, and permanent methods. The tubal sterilization methods will generally need to be performed in an operating room under anesthesia. Tubal sterilization can be performed postpartum either immediately after a c-section or vaginal delivery or scheduled as an outpatient procedure. The vasectomy can be done as an office procedure under local sedation if necessary. Generally, there are very few contraindications for tubal sterilization and vasectomy. The sterilization methods are intended to be irreversible. Most people who choose sterilization are satisfied with their decision. There is a small proportion of women who regret a tubal sterilization procedure. Among men, there also is a small percentage that does experience regret as well [33]. It is essential that men and women receive appropriate consulting about the permanency of sterilization, including the risks, benefits, and alternatives.

Natural Family Planning

Natural family planning mainly consists of fertility based methods (FAB) to identify the fertile days of the menstrual cycle. This can be done by observing fertility signs such as cervical secretions, and basal body temperature or by monitoring cycle days. The FAB methods can be used alone or in combination with barrier methods.

Effectiveness: It is unclear how effective natural family planning is. The comparative efficacy of fertility awareness-based methods remains unknown [34].

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Vulvovaginitis and Cervicitis

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Charles Fleischer and Shermeeka Hogans-Mathews

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Acute Cervicitis

The appearance of a normal cervix varies widely throughout a woman's lifespan. As estrogen levels rise during puberty, columnar endocervical cells evert onto the squamous ectocervical epithelium at the squamocolumnar junction (metaplasia) and create a transformation zone. This site may be

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red and friable and can be the source of postcoital and intermenstrual bleeding. During and after menopause, this squamocolumnar junction generally recedes into the endocervical canal and the cervix becomes atrophic with a pale appearance. Subepithelial point hemorrhages may also be seen, and it becomes susceptible to trauma [1]. Cervicitis is inflammation of the uterine cervix that primarily affects the columnar epithelial cells of the endocervical glands but may also affect the squamous epithelial cells of the ectocervix. There are two major diagnostic signs characteristic of cervicitis in which either one or both may be present. These signs include a purulent or mucopurulent endocervical exudate in the endocervical canal or on an endocervical swab and sustained endocervical bleeding induced by gentle palpation or passage of a cotton swab through the cervical os [2].

Cervicitis is usually acute, and well-established etiologies include sexually transmitted infections (STIs), such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Herpes Simplex Virus* (HSV), *Trichomonas vaginalis*, and *Bacterial vaginosis* (BV). Acute cervicitis may be caused by other infectious agents such as rarer bacteria, viruses, and fungi [1]. Allergens or idiopathic inflammation should also be considered. Cervical infection can ascend (upper-genital-tract infection) and cause endometritis or pelvic inflammatory disease (PID). Therefore, women with cervicitis should be tested for both *Chlamydia trachomatis* and *Neiserria gonorrhoeae* with nucleic acid amplification tests (NAATs) using vaginal, cervical, or urine samples. With cervicitis, BV and Trichomonas should also be tested for and treated if present [2].

Both *Neisseria gonorrhoeae* and *Chlamydia trachomatis* produce varying degrees of an acute inflammatory reaction that affects the glandular epithelium. In a 2018 surveillance report by the Centers for Disease Control and Prevention (CDC), there were 1.8 million cases of Chlamydia, which is the most frequently reported infectious disease, and 583,405 cases of Gonorrhea [3]. Infections can be diagnosed through the assessment of first-catch urine or swab specimens from the endocervix, vagina, or urethra. However, NAATs, which have been cleared by the FDA for provider or self-collected samples from vaginal swabs (equivalent in sensitivity and specificity) [4], have replaced cultures as the gold standard [5]. The sensitivity is usually above 90% and the specificity is around 99%, which contributes to a 20–50% greater detection of *C. trachomatis* infections compared to cultures [4].

As for genital herpes, most recurrent cases are caused by HSV-2 with approximately 50 million persons in the United States infected [6]. Many of these individuals have mild or unrecognized infections but shed the virus intermittently in the anogenital area. Therefore, they can be transmitted by persons who are either unaware that they have the infection or are asymptomatic when transmission occurs [7]. The selected diagnostic test will vary with the overall clinical presentation and can include a viral culture, polymerase chain reaction (PCR), type specific serologic tests, or direct fluorescence antibody [8]. In a patient with active lesions, cell culture and PCR are the preferred tests. The sensitivity of viral culture is low, especially for recurrent lesions, and declines rapidly as lesions begin to heal. NAAT, again, is more sensitive compared to viral cultures, but negative results do not rule out an infection as viral shedding is intermittent [7].

An estimated five million women in the United States are infected annually with Trichomonas [9, 10], and like genital herpes, this may be an underestimate as up to 50–75% of cases are asymptomatic [9, 11] and therefore unreported. *Trichomonas vaginalis* is the cause of approximately 10% of all cases of vaginitis; if left untreated, it may progress to urethritis or cervicitis. Trichomoniasis is also associated with coinfection with other sexually transmitted organisms [9] and is the most common sexually transmitted infection in the world, with 120 million cases reported each year [12]. Microscopy is often the first step in the diagnosis of trichomoniasis due to the convenience and low cost, as well as sensitivity of 60%–70% and specificity of nearly 100% [13, 14]. If trichomonads are visible on microscopy, no further testing is indicated as

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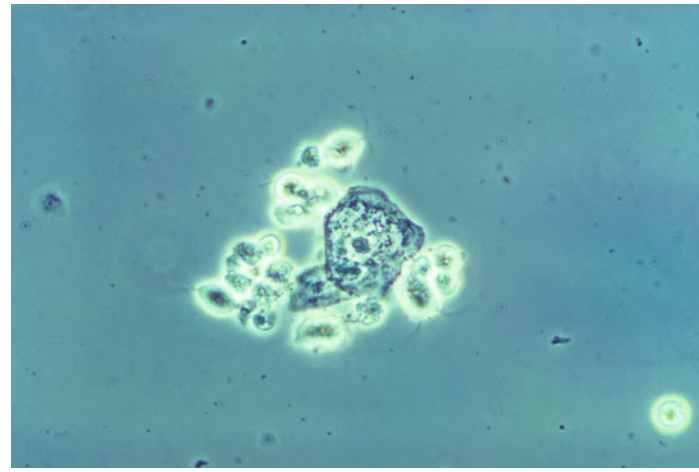


Image 1 *Trichomonas vaginalis* parasitic protozoa. This image shows a wet prep microscopy from a vaginal specimen showing trichomonads in a patient presenting with vaginal symptoms. (Obtained from the Centers for Disease Control and Prevention. 1975. Public Health Image Library ID# 17912. https://phil.cdc.gov/Details.aspx?pid= 17912)

seen on Image 1. However, if microscopy is negative, then the gold standard NAAT with high sensitivity and specificity is performed as opposed to using rapid diagnostic kits, or a culture where results may take up to seven days. For example, the Aptima T. vaginalis assay (Hologic) that has been approved by the US Food and Drug Administration (FDA) has a sensitivity that ranges from 95 to 100 percent and a specificity that ranges from 95 to 100 percent that is superior to other diagnostic tests in all patient populations via vaginal discharge and urine samples [15–18]. It often detects three to five times more *T. vaginalis* infections compared to wet-mount microscopy, which has a sensitivity of 51 to 65 percent. Other NAATs include Amplicor (Roche), AmpliVue (Quidel), BD ProbeTec TV Qx (BD Diagnostics), NuSwab VG (LabCorp), Solana (Quidel), and Xpert TV (Cepheid) assays [19].

Another bacterial cause of cervicitis is *Bacterial vaginosis*, which commonly results in vaginal discharge in women of reproductive age with prevalence ranging from 10% to 50% [20–22]. It is thought to arise when anaerobic vaginal flora overtakes and/or replaces the aerobic vaginal flora, namely, lactobacilli. Typically, *Gardnerella vaginalis* and mycoplasma are increased in number, while lactobacilli comprise a smaller fraction. The exact cause of BV is not clear. However, *G. vaginalis* alone is the most frequent cause and makes up approximately 40% of BV cases, followed by other anaerobes which include *Mycoplasma hominis, Peptostreptococcus spp.*, and *Mobiluncus spp.* [21–23]. Women with BV are also at a higher risk of acquiring a sexually transmitted disease (STD), such as HIV, gonorrhea, and chlamydia [24, 25]. A diagnosis of BV is established primarily using the Amsel criteria [26], wherein three of the following four criteria have to be met to diagnose BV. The criteria include: Gray, homogeneous discharge; positive amine (fishy) odor or "whiff test" (positive potassium hydroxide (KOH test) – sensitivity 6.58% and specificity 73.6%); vaginal pH $>$ 4.5; $>$20% clue cells/HPF on microscopy (sensitivity 43.1% and specificity 99.6%) [27]. See Image 2. Cultures are of limited diagnostic value as cultures for *G. vaginalis* in almost all women with symptomatic infections are positive, whereas 50%–60% of healthy asymptomatic women are also positive [12]. The FDA has approved commercial tests that have acceptable performance compared to gram staining, which include a DNA probe-based test for high concentrations of *G. vaginalis* (BD Affirm VPIII), vaginal fluid sialidase activity test (OSOM BVBlue test), and two PCR-based assays that target several BV-associated species (BD Max, Aptima BV).

Lately, *Mycoplasma genitalium* has been increasingly associated with acute cervicitis and an infection can lead to (PID), endometritis,

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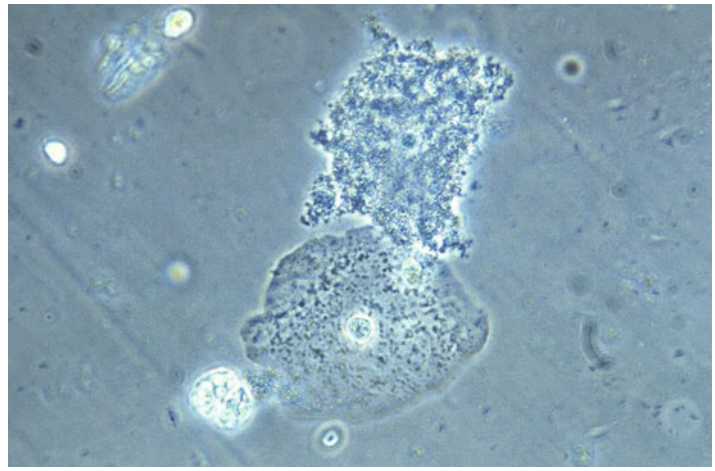


Image 2 Clue cell. This image shows wet prep microscopy from a vaginal specimen showing a clue cell in a patient presenting with bacterial vaginosis. (Obtained from the Centers for Disease Control and Prevention. 1978. Public Health Image Library ID# 14574. https://phil.cdc.gov/Details.aspx?pid=14574)

increased risk of HIV transmission, and complications of both pregnancy and childbirth [28, 29]. When a patient's sexual partners are affected, there is also increased economic and emotional burden [1]. *Mycoplasma genitalium* is very difficult to culture, and patients are often asymptomatic [2]. NAAT with PCR or transcription-mediated amplification is therefore used in research facilities and laboratories and may be available for high-risk populations [28, 30]. A prospective multicenter clinical study published in 2019 demonstrated clinical efficacy for the first FDA-cleared transcription-mediated amplification (TMA) NAAT for the detection of *M. genitalium* 16S rRNA [30]. Depending on the specimen, sensitivity and specificity estimates ranged from 77.8% to 98.9% and 97.8% to 99.6%, respectively. However, study limitations include the lack of oropharyngeal or rectal samples and coinfection data for other STIs. Future studies will be needed to further evaluate its role in asymptomatic populations.

A majority of patients with acute cervicitis are asymptomatic and cases are detected incidentally on examination. As intervals for routine gynecologic screening examinations lengthen, cervical infections, especially if asymptomatic, may be missed. Annual wellness examinations and other patient visits outside of routine gynecologic cancer screening visits should, if indicated, include a brief evaluation with a sexual risk assessment and a gynecologic examination. All patients being evaluated for chlamydia, gonorrhea, or trichomoniasis should also be offered counseling and testing for HIV and syphilis [7].

Chronic Cervicitis

Unlike the more common acute cervicitis, chronic cervicitis is characterized by persistent discharge for at least three months despite the resolution or exclusion of infection [31]. Chronic cervicitis is also usually caused by noninfectious sources, and there is no standard approach to these cases. Noninfectious causes include mechanical or chemical irritation, radiation therapy, systemic inflammatory diseases (such as Behcet syndrome), and malignancy [2]. Chronic cervicitis may remain idiopathic in many women due to unknown or undetectable infectious and non-infectious agents.

Noninfectious causes of both acute and chronic cervicitis include allergens and irritants. Commercial products that can irritate or disrupt the cervicovaginal mucosa include spermicides and contraceptive creams, douching, perfumes, and deodorants. These irritants can disrupt the normal balance of vaginal flora and lead to cervicitis [1]. Irritants also include latex, povidone-iodine, surfactants, topical anesthetics, and cornstarch. Mechanical irritation, caused by trauma from surgical instruments and foreign bodies such as a pessary, diaphragm, tampon, cervical cap, or condom, can also cause cervicitis [2].

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Office Evaluation

When approaching a patient with cervicitis, in addition to a focused medical history, visual and olfactory characterization of the discharge, microscopy, pH value of the secretions, and a gynecological examination should be performed. Focused questions should cover vaginal itching or pain, characterization of any discharge (amount, consistency, color, odor), menstrual cycle status, and intermenstrual or postcoital bleeding (Fig. 1). A thorough medication history should focus on antibiotic use, hormones, and any over-the-counter products [31]. Clinicians need to sensitively and appropriately screen for STI risk factors by asking about the patient's symptoms, the partner's symptoms, and a detailed sexual history [1].

Findings present on a cervical examination in a patient with cervicitis may include mucopurulent discharge, cervical friability with sustained easy bleeding when gently palpated or swabbed, vesicular or ulcerative lesions, punctate hemorrhages of the "strawberry" cervix, and cervical motion tenderness (CMT). Diffuse vesicular lesions or ulcerations suggest HSV, while punctate hemorrhages are characteristic of *T. vaginalis*. Condyloma lesions may have a flat, raised, or cauliflower appearance. On bimanual examination, CMT caused by inflammation of the pelvic ligaments is a clear indication of PID which can complicate cervicitis. During the examination, clinicians

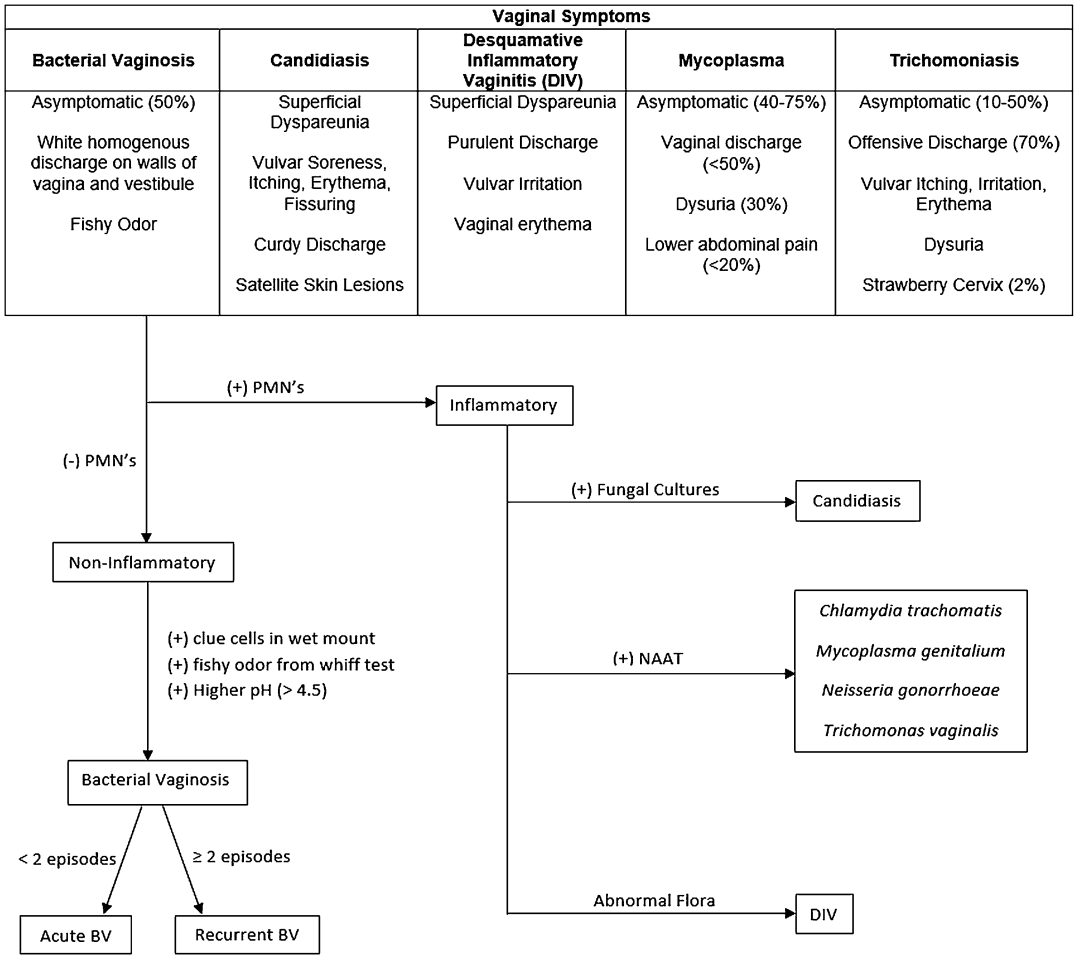


Fig. 1 Approach to the patient with cervicitis

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Table 1 Common causes of vaginal discharge with concomitant cervicitis

Bacterial vaginosis	Aerobic vaginitis	Candidiasis	Trichomoniasis
50% asymptomatic	10–20% asymptomatic	60% of women colonized Minority develop symptoms	10–50% asymptomatic 5–15% no abnormal signs
Thin white homogenous discharge, coating walls of vagina and vestibule Offensive fishy odor	Purulent discharge	Vaginal discharge may be curdy	Offensive vaginal discharge in up to 70% Frothy and yellow-green discharge in 10–30%
Absence of vaginitis	Vulval burning or stinging Superficial dyspareunia Vaginal erythema and edema Vaginal ulceration	Vulval soreness, itching, and erythema Vulval fissuring Superficial dyspareunia Satellite skin lesions Vulva edema	Vulva itching/irritation and erythema Dysuria Rarely low abdominal discomfort Vaginitis 2% strawberry cervix visible to naked eye

Obtained from Sherrard J, Wilson J, Donders G, Mendling W, Jensen JS. 2018 European (IUSTI/WHO) International Union against sexually transmitted infections (IUSTI) World Health Organisation (WHO) guideline on the management of vaginal discharge. Int J STD AIDS. 2018;29(13):1258–1272. doi:https://doi.org/10.1177/0956462418785451

should also look for noninfectious causes including abrasions and ecchymosis [1]. When indicated, they should perform smears, cultures, or immunofluorescence assays to confirm or exclude an infection with *N. gonorrhea* or chlamydia [31].

Vaginal discharge concomitant with cervicitis is more commonly caused by infections (up to 90%) such as STIs, with the alteration of vaginal flora resulting in an increase in colonization by different facultative pathogenic microorganisms (i.e., *Gardnerella vaginalis*). These infections include bacterial vaginosis (up to 40%–50% of cases), vulvovaginal candidiasis (20%–25%), and trichomoniasis (15%–20%) **(**Table 1**)**. If an infectious process is suspected, a sample of the vaginal discharge should be taken from the posterior vaginal vault using a cotton-tipped applicator and smeared on a glass slide, followed by a droplet of 0.9% normal saline. The slide is then evaluated using phase-contrast wet mount microscopy [12]. Compared to real-time PCR, wet mount sensitivity is 40% (95% confidence interval, 19.1% to 63.9%) and specificity is 100% (95% CI, 99.7% to 100%);[19] therefore, if a patient is symptomatic with cervicitis, further testing should be performed using culture or NAAT. A leukocyte-rich urethral or cervical discharge specifically is considered highly suggestive of an infection. With negative detection of trichomonads and greater than 10 white blood cells per high power field seen on microscopy of vaginal fluid, this may indicate a *Chlamydia trachomatis* or *Neiserria gonorrhoeae* infection [2]. A gram stain is also essential as composition of the microbial flora and the purity can be obtained [12].

Treatment

Treatment of cervicitis is directed at etiology and symptomatology. When the etiology is unknown, there is no recommendation for treatment beyond empiric coverage for STIs. Empiric coverage can be provided for women who are found to be at an increased risk for *Chlamydia trachomatis* or *Neiserria gonorrhoeae* infection while considering the feasibility of follow-ups or NAAT [2].

First line empiric treatment is made up of single doses which should be administered upon the visit to increase adherence and is comprised of azithromycin 1 gram orally and ceftriaxone 250 milligrams intramuscularly as this covers for chlamydial, gonorrheal, and mycoplasma infections and is a safe option for pregnant women

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[2]. Depending on patient presentation, such as QTc prolongation or hepatotoxicity, azithromycin may be substituted by doxycycline 100 milligrams twice daily for seven days. However, one should be aware that there is a higher prevalence of gonococcal resistance with tetracyclines in the United States. Despite sharing a beta-lactam ring, as the third generation cephalosporins have such a different side chain compared to penicillin, the chances of cross-reactivity are close to 0% [32]. However, if seriously concerned, a clinician may consider using a fluoroquinolone as an alternative to the cephalosporin. Expedited partner therapy should also be provided, and patients should be counseled on abstinence or safe sex practices for seven days after completion of therapy. If cervicitis persists on follow up even after standard treatment of sexually transmitted infections, clinicians would need to consider the cause being *Mycoplasma genitalium*. [1]

As for genital HSV, management should focus on the chronic nature of the disease as well as acute recurrences, which entails the use of antivirals for a minimum of seven to ten days [7]. Valacyclovir may be the preferred antiviral compared to others that require dose administration three to five times a day. Smaller doses of these agents are used for suppressive therapy for those who have experienced more than four to five recurrences per year, and it has successfully reduced recurrence rates by 70%–80%. However, clinicians should periodically assess for discontinuation as recurrences tend to diminish over time.

Treatment of BV in the presence or absence of pregnancy consists of clinically equivalent metronidazole or clindamycin [7]. Although oral and vaginal formulations have similar clinical cure rates of 70–80%, the vaginal preparation is preferred due to less systemic side effects. However, drug and formulation selection should be patient-specific by evaluating drug availability, adverse effects, and previous response to therapies. Metronidazole is available as 500 mg orally twice daily for 7 days, or as a 0.75% vaginal gel with one applicatorful of 5 g (equivalent to 37.5 mg of metronidazole) inserted once daily for a total of 5 days [14]. A one-time administration (orally and vaginally) is less effective, and therefore not recommended [7]. For clindamycin, a 7-day course of 2% clindamycin cream vaginally (5 g of cream contains 100 mg of clindamycin phosphate) may be used. Alternative regimens include oral clindamycin (300 mg twice daily for seven days), clindamycin ovules (100 mg intravaginally once daily for three days), and single application of clindamycin (Clindesse) as a bioadhesive. These regimens have not been studied extensively and may have lower efficacy for eradicating BV [14]. BV resolves spontaneously in about 30% of pregnant and nonpregnant women, but treatment may reduce the risk of acquiring other STDs. During pregnancy, BV is particularly harmful due to the possibility of a peripartal infection and premature birth. Therefore, regardless of pregnancy status, symptomatic and asymptomatic women should be treated [12]. Recurrent BV treatment is discussed below.

Follow-up

A follow-up visit should be scheduled to allow the provider to determine whether the cervicitis has resolved. Women with a specific diagnosis of chlamydia, gonorrhea, or trichomonas should be offered partner services and instructed to return in three months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated [33]. Test-of-cure to detect therapeutic failure for chlamydia or uncomplicated gonorrhea (i.e., repeat testing 3–4 weeks after completing therapy) is not advised for persons treated with the recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected. If symptoms persist or recur, women should be instructed to return for re-evaluation. Retesting is not the same as a test-of-cure (TOC). Retesting for reinfection of chlamydia, gonorrhea, and trichomonas is done routinely. A test-of-cure, however, is performed three to four weeks after treatment and only under the following circumstances: (1) if concern exists regarding persistence of infection despite treatment, (2) if symptoms of

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infection persist, (3) if lack of adherence to the treatment regimen is suspected, and (4) after treatment of chlamydia during pregnancy [7].

Women with persistent or recurrent cervicitis despite treatment should be reevaluated for possible re-exposure or treatment failure to gonorrhea or chlamydia. If relapse and/or reinfection with a specific STD has been excluded, BV is not present, and sex partners have been evaluated and treated, the management options for persistent cervicitis are undefined; in addition, the utility of repeated or prolonged administration of antibiotic therapy for persistent symptomatic cervicitis remains unknown [7].

The etiology of persistent cervicitis, including the potential role of *M. genitalium,* is unclear. *M. genitalium* might be considered for cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy in which re-exposure to an infected partner or medical nonadherence is unlikely. In settings with validated assays, women with persistent cervicitis could be tested for *M. genitalium* with the decision to treat with moxifloxacin based on results of diagnostic testing [34]. In treated women with persistent symptoms that are clearly attributable to cervicitis, a referral to a gynecologic specialist can be considered [7].

Special Populations

For cervicitis among special populations, although women with the infection and HIV require the same therapy as those without HIV, treatment is more crucial to reduce cervical HIV shedding and subsequent transmission. The diagnosis and treatment of cervicitis is also the same for pregnant women [7].

Vaginitis

Vaginitis broadly includes conditions that can cause an array of symptoms ranging from discharge, itching, burning, odor, swelling, and more [35]. Vaginitis contributes to many of the gynecological visits to the primary care office. 70% of cases of vaginitis are caused by BV, trichomoniasis, and vulvovaginal candidiasis (VVC) [36]. Vaginitis can be divided into two separate categories: inflammatory versus noninflammatory (Table 2) [35]. Inflammatory vaginitis involves the presence of vulvar/vaginal edema and erythema or the microscopic presence of polymorphonuclear neutrophils (PMNs). Noninflammatory vaginitis is the absence of the above characteristics [35].

Inflammatory Vaginitis

Trichomoniasis

As discussed earlier in the cervicitis section of this chapter, *Trichomoniasis* is the most common cause of inflammatory vaginitis [35]. Similar to BV, there is a higher prevalence of *Trichomoniasis* in African-American women (9.6%) compared to non-Hispanic white women (0.8%) [35, 42]. Diagnostic testing was discussed previously; however, it is important to note that Trichomoniasis cannot be diagnosed via Papanicolaou tests (liquid-based or conventional) due to false-positive and false-

Table 2 Classifications of vaginitis

Vaginitis [35]		
Inflammatory	Most common	Least common
	Trichomoniasis Vulvovaginal Candidiasis (VVC)	Atrophic vaginitis or genitourinary syndrome of menopause (GSM) Desquamative inflammatory vaginitis (DIV)) Multimucosal erosive diseases (autoimmune)
Noninflammatory	Most common	Least common
	Bacterial vaginosis (BV)	Vulvovaginal Candidiasis (certain forms) Mixed infections (VVC/BV)

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negative results [35]. Retesting at 3 months is recommended by the CDC to due high rates of recurrence but can be performed as early as one month after treatment [35].

Vulvovaginal Candidiasis

In their lifetimes, 70–75% of women are expected to experience at least one episode of VVC [37]. Out of this population, 10–15% are estimated to be asymptomatic colonizers and 5–10% will potentially experience recurrent VVC [37]. The symptoms of VVC including gynecological discomfort, pain, irritation, and hinderances to sexual interactions can cause a great deal of distress including mental anguish and lowered self-esteem [37]. Sequelae of untreated VVC infections include PID, ectopic pregnancy, infertility, spontaneous abortions, changes in menstruation, and increased HIV susceptibility [37].

Factors that contribute to the pathogenicity of Candida can be attributed to its hyphae formation, adhesion, phenotypic switching, extracellular hydrolytic enzyme production, and formation of biofilm [37]. Risk factors for candida infection include uncontrolled diabetes, pregnancy, hormone replacement therapy (HRT), corticosteroid use, and antibiotics are noted to be risk factors related to host [37]. In addition to the risk factors discussed, intrauterine devices, condoms, oral contraceptives, spermicides, clothing habits (i.e., tight-fitting underwear), hygiene, and sexual activity can also contribute to increasing risk of VVC infection [37]. HRT with estrogen and progesterone also seem to play a role in increasing VVC infection. The incidence of VVC in females prior to puberty and after menopause appears to be uncommon [37]. VVC is often seen in pregnancy when the following contributors are present: high carbohydrate diets, immune system suppression, and stress [37]. Receptive oral sexual activity and frequent sexual intercourse have been implicated as proposed risk factors in recurrent VVC [37].

The most common species of VVC include *C. albicans, C. glabrata, Candida krusei, Candida parapsilosis,* and *Candida tropicalis* [37]. There is a concern for resistance as there has been an increase in C. *glabrata* due to prolonged antifungal treatments and self-medication. *C. glabrata* is more resistant to antifungal medications [37]. Thus, appropriate examination, diagnosis, and treatment of VVC are strongly recommended versus prolonged treatment or recurrent self-treatment. Fortunately, flucytosine and boric acids, which are nonazole antifungals, have been successful at treating *Non-Candida albicans Candida (NCAC)* [37].

VVC can be classified as either uncomplicated or complicated. There are four specific criteria for uncomplicated VVC infection which include the following: nonimmunocompromised status, mild-to-moderate symptoms or findings, *Candida albicans* infection (proven or suspected), and sporadic or infrequent episodes of less than 4 each year [15]. Conversely, classification of *complicated VVC* involves meeting at least one of the following criteria: immunocompromising disease states such as diabetes, severe symptoms, or findings which include fissure formation, extensive erythema of the vulva, and excoriation or recurrent episodes defined as greater than or equal to four episodes in one year, or NCAC (proven or suspected) [15].

Diagnosis of VVC

Abnormal discharge is highly associated with VVC with most patients complaining of a white cottage-cheese-like discharge [40]. Two findings are usually required to diagnose VVC: (1) Aptima test positive for *Candida* or positive fungal vaginal culture or (2) wet-mount microscopy with hyphae, pseudohyphae, or spores present [40]. Unfortunately, the sensitivity of microscopy in identifying VVC is only 50–70% and may not yield the correct diagnosis if the patient has already begun over-the-counter (OTC) treatment with an antifungal prior to vaginal examination [40].

Treatment of VVC

Uncomplicated vulvovaginal candidiasis can be treated with OTC intravaginal medications, prescription intravaginal medications, or prescribed

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oral agents. Intravaginal treatment options may include application of 5 g of OTC clotrimazole 1% cream once daily for 7–14 days, clotrimazole 2% cream once daily for 3 days, miconazole 2% cream once daily for 7 days, or miconazole 4% cream for 3 days [14, 15]. Other OTC options include miconazole vaginal suppositories in 100 mg (7 day), 200 mg (3 day), and 1200 mg (1 day) dosages or application of tioconazole 6.5% ointment in a 5 g single dosage [14]. Prescribed intravaginal creams and suppositories include butoconazole 2% cream single dose, terconazole creams in 0.4% for 7 days and 0.8% for 3 days in 5 g dosages and an 80 mg vaginal suppository of terconazole for 3 days [14]. Fluconazole is available as a single 150 mg dose oral agent which can be repeated in 72 hours, if needed, and carries the risk of hepatotoxicity [14]. Medication reconciliation and checking for drug-drug interactions is also of paramount importance prior to prescribing fluconazole.

Noninflammatory Vaginitis

Bacterial Vaginosis

Bacterial vaginosis (BV)), which was discussed earlier in the cervicitis section, is a non-inflammatory type of vaginitis and causes up to 30–50% of vaginitis cases [35, 36]. After adjustments are made for poverty, age, and education, ethnic minorities (African-Americans and/or American-Hispanic women) are up to 3 times more likely to have BV than in white non-Hispanic women [35]. Risk factors for recurrence of BV include having a regular sex partner (especially in female to female intercourse) and a history of BV infection [38]. Almost 60% of women will have a recurrence of BV within 12 months after a single treatment. The recurrence may be due to a bacterial biofilm. [35]. Currently, the CDC does not recommend the usage of probiotics in preventing BV infections or recurrences [35]. However, consistent condom use has been shown to decrease BV incidence [35]. Recurrent BV has many psychological, social, and financial implications for patients whom often present in despair and frustration about recurrent infections given the accompanied discharge, odor, and discomfort. Thus, it appears that recurrent BV can certainly take its toll on patients by causing moderate-to-severe impact on overall quality of life and interfering with their sexual functioning and self-esteem [39]. List 1 explores treatment options for recurrent bacterial vaginosis.

List 1 Recurrent Bacterial Vaginosis Treatment

Treatment options for recurrent bacterial vaginosis [35, 39]
Intravaginal metronidazole daily × 10 days, then twice weekly for 4–6 months [35]
Oral tinidazole or metronidazole twice daily × 7 days, then intravaginal boric acid 600 mg daily × 21 days, then intravaginal metronidazole twice weekly for 4–6 months [35]
Secnidazole 2 g single dose [39]

Atrophic Vaginitis or Genitourinary Syndrome of Menopause (GSM)

Atrophic vaginitis, also known as GSM, affects greater than 50% of postmenopausal women [41]. Patients often present with symptoms that include sexual dysfunction, dyspareunia, vaginal dryness, increased urinary frequency and urgency, vaginal itching and urinary tract infections [41]. Given the fact that primary care physicians may not screen for GSM and that patients may be hesitant to mention symptoms due to embarrassment, this condition often remains untreated and undiagnosed [41]. GSM is a clinical diagnosis that usually presents with the following examination findings: scarce pubic hair, atrophy of labia minora and vaginal canal, pale mucosa, increased vaginal pH, and narrowing of the introitus [41]. Etiologies other than GSM should be considered, such as dermatoses, malignancies, irritants, inflammatory diseases, or infectious vaginitis [41].

Short-term treatment options for GSM include lubricants and moisturizers. Water-based lubricants are recommended compared to silicone,

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petroleum, and oil-based lubricants. Silicone lubricants have increased risk of genital issues, whereas petroleum and oil-based lubricants can increase the risk of BV and VCC infections [41]. Another option is hyaluronic acid-based vaginal gel which has been shown to improve symptoms of dryness and can be used every 3 days [41]. If prescription therapy is needed, low-dose vaginal estrogen therapy (ET) is recommended, especially due to its efficacy and safety profile compared to systemic estrogen [41]. Low-dose vaginal treatment options include creams, inserts, and vaginal rings. Creams include estradiol-17β (Estrace) and conjugated estrogens (Premarin) both dosed at 0.5–1 g daily for two weeks and progressing to 0.5–1 g one to three times weekly [41]. Vaginal inserts include estradiol hemihydrate (Vagifem, Yuvafem) dosed at 10-μg inserted once daily for two weeks and progressing one insert twice weekly and DHEA (Intrarosa) dosed at 6.5 mg once daily [41]. Vaginal rings include estradiol-17β (Estring) and estradiol acetate (Femring) with instructions to place insert and leave in for 90 days before replacement [41]. Lastly, selective estrogen receptor modulators (SERM), such as Ospemifene (Osphena), are dosed at 60 mg daily and are approved for moderate to severe dyspareunia [41]. Of note, the safety of this medication has not been determined in patients who are at a higher risk for breast cancer as no data has suggested that Osphena stimulates breast tissue [41]. Of note, it may take a few weeks for patients to notice full benefits of therapy. Also, endometrial protection with a progestogen is usually not needed when women are being treated with low-dose vaginal estrogen therapy [41].

Desquamative Inflammatory Vaginitis (DIV)

Often heralded as a diagnosis of exclusion, DIV is a process of chronic inflammation of the vestibule and vagina that is usually seen in white (non-Hispanic) women and perimenopausal women [35]. Etiology of DIV is unclear. However, a lichen planus variant or a vaginal atrophic bacterial overgrowth may be considered potential sources [36]. Characteristic patients usually present in a hypoestrogenic condition with yellow or brown abnormal discharge, severe dyspareunia, and burning [36]. The clinical hallmark of DIV entails microscopic findings of PMNs, inflammatory cells, and parabasal epithelial cells, in addition to increased vaginal pH and purulent discharge [35]. Upon examination, extraneous vaginal discharge and severe erythema of the vagina and introitus are present [36]. Of note, vaginitis related to estrogen and infectious etiologies must be excluded prior to arriving at the diagnosis of DIV [35]. Trials of clindamycin or intravaginal steroids are treatment options. These include Clindamycin vaginal cream 2% every other night, and hydrocortisone 10% vaginal suppository or hydrocortisone 25 mg suppositories every night [35]. Prolonged therapy for 4–8 weeks is often needed to resolve symptoms [35].

Other Causes of Inflammatory Vaginitis

Other causes of inflammatory vaginitis include lichen planus, pemphigus vulgaris, pemphigoid, and cicatricial pemphigoid. One of the hallmarks of these disorders includes erythematous, shallow, and isolated erosions of the vagina or labia minora [35]. Biopsy is warranted in these cases. For patients with these symptoms, referrals are often necessary to gynecology or dermatology.

Cytolytic vaginosis is caused by Lactobacilli overgrowth which is noted to cause cellular dissolution due to damages of the epithelium of the vagina [38]. This is usually most problematic during the luteal phase of the menstrual cycle [38]. Vulvar dysuria, pruritis, dyspareunia, and erythema with white pasty appearing vaginal walls are hallmark symptoms of cytolytic vaginosis. [39]. Wet prep would reveal lactobacilli and fragmented squamous cells with the absence of leukocytes, yeast, clue cells, and trichomonads [39]. Sodium bicarbonate treats cytolytic vaginosis by raising the pH of the vagina. This can be done as a prepared douche or with a gelatin capsule containing sodium bicarbonate [39].

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Approach to the Patient

Obtaining a thorough list of symptoms, sexual history, history of prior vaginal infections as well as hygiene history is important in assisting in workup of vulvovaginitis. Recommendations include obtaining a focused history, performing an adequate gynecological exam (vulva, vestibule, vagina, and cervical inspection) with either testing of vaginal pH, microscopy of vaginal secretions, and amine test or utilizing Aptima test swab for further testing [36]. Patients presenting with concerns for vaginitis may experience an array of adverse emotional and psychological sequelae. Patients may be significantly impacted, leading to sexual dysfunction, decreased self-esteem or negative thoughts of self, frustration, loss of productivity from educational or occupational pursuits, decreased socialization, and effects from pain, discomfort, and inconvenience [38]. For a majority of patients, there can be a host of social issues that arise given the sensitivity involved with gynecological issues. Building rapport with patients and being sensitive, empathetic, and respectful during encounters can help place patients at ease and result in a more productive encounter. Patients with recurrent or abnormal symptoms and issues should be referred to the gynecologist for further evaluation and management.

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Menstrual Disorders

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Sabrina Hofmeister and Seth Bodden

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Patients frequently bring forth concerns about disorders of menstruation to primary care providers. These disorders are complex and often have many plausible etiologies. A sound knowledge of anatomy and physiology is necessary to definitively diagnose and manage these conditions. This chapter will outline the etiology, diagnosis, and treatment of some of the most common menstrual disorders which are frequently addressed by family physicians.

Premenstrual Disorders

Premenstrual disorders (PMD) are conditions that occur during the luteal phase and resolve shortly after menstruation. Roughly 80% of menstruating women report symptoms during the luteal phase, and between 2% and 5% of women meet the diagnostic criteria for a premenstrual disorder [1]. The subspecialties of psychiatry and gynecology have developed overlapping but distinct diagnoses that qualify as premenstrual disorders. Premenstrual syndrome (PMS) was defined by

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Table 1 Diagnostic criteria for premenstrual syndrome

Premenstrual syndrome		Premenstrual dysphoric disorder	
Affective symptoms	Somatic symptoms	Column A	Column B
Anger outbursts	Abdominal bloating	Affective lability	Decreased interest in usual activities
Anxiety	Breast tenderness	Irritability or anger	Difficulty concentrating
Confusion	Breast swelling	Depressed mood	Lethargy or lack of energy
Depression	Headache	Anxiety, tension	Change in appetite or overeating
Irritability	Joint or muscle pain		Sleep changes
Social withdrawal	Extremity swelling		Feeling overwhelmed
	Weight gain		Somatic symptoms (see column 2)

the field of OB/GYN and consists of both affective and somatic symptoms. Premenstrual dysphoric disorder (PMDD) was defined by the field of psychiatry and focuses primarily on psychiatric symptoms in its diagnostic criteria.

In order to diagnose a premenstrual disorder, symptoms must occur during the luteal phase and resolve shortly after the onset of menstruation. Other conditions may have symptoms that worsen during the luteal phase, but these can be distinguished from PMD because some symptoms persist throughout the menstrual cycle [1]. When working up a PMD, differential diagnoses should contain conditions that could be worsened in the luteal phase such as depression, anxiety, migraines, endometriosis, and hypothyroidism. A diagnosis of PMS can be made if the patient reports at least one affective and one somatic symptom in the 5 days preceding menses (Table 1). This must have occurred during at least the last three menstrual cycles and symptoms must resolve within 4 days from the onset of menstruation independent of any external pharmacologic therapy. Symptoms must be severe enough to impair functioning in social, academic, or work settings and must occur reproducibly during at least two cycles of reporting [2]. A diagnosis of PMDD may be made if, in the majority of menstrual cycles, at least five symptoms from a combination of both columns (Table 1) are markedly present in the final week before the onset of menses. The symptoms must have been present for the majority of menstrual cycles in the last year and have caused significant distress and alternation in functioning in all relationships and settings. The symptoms must also not be attributable to other medical or psychiatric conditions or pharmacologic treatments and must improve within a few days after initiation of menses with resolution within a week after menses subside [3].

Because women tend to overestimate the cyclical nature of their symptoms, prospective questionnaires are the most accurate way to diagnose PMS and PMDD [1]. The Daily Record of Severity of Problems (DSRP) seen in Fig. 1 is a valid and reliable tool that can be used to diagnose PMS or PMDD. The DSRP has women rate their symptoms through at least two menstrual cycles. Alternatively, women can administer the DRSP on the first day of their menses if a faster diagnosis is desired.

SSRIs are the first-line treatment for severe symptoms of PMS and PMDD. Sertraline, paroxetine, fluoxetine, citalopram, and escitalopram can be used to treat both the psychiatric symptoms and physical symptoms of PMS and PMDD. A 2013 Cochrane review found that each of the five SSRIs studied had statistically significant benefits on patient-reported symptoms when compared to placebo. Either continuously taking an SSRI or taking it only during the luteal phase has been shown to be beneficial. Higher doses tend to be needed for relief of physical symptoms. Bupropion was not effective for symptom relief of PMS or PMDD. SNRIs such as venlafaxine have been used off-label to treat PMDD [1].

Studies have shown that continuous use of OCPs can provide benefit when treating physical and psychiatric symptoms of PMS and PMDD. It appears that OCPs may be most beneficial in treating the psychiatric symptoms of PMDD; however, there is evidence that OCPs may improve abdominal bloating, mastalgia, headache, weight gain, and swelling of the extremities. Small studies have shown calcium supplementation with calcium

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Daily Record of Severity of Problems for Diagnosis of Premenstrual Dysphoric Disorder

Symptoms	Day of menstrual cycle (day 1 is the start of the menstrual period)																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Felt depressed or sad																																			
Felt hopeless																																			
Felt worthless or guilty																																			
Felt anxious or tense																																			
Had mood swings																																			
Feelings were more easily hurt																																			
Felt angry or irritable																																			
Had conflicts with people																																			
Had less interest in activities																																			
Had trouble concentrating																																			
Felt tired or lacked energy																																			
Had increased appetite																																			
Had food cravings																																			
Slept more or had trouble waking up																																			
Had trouble getting to sleep or staying asleep																																			
Felt overwhelmed																																			
Felt out of control																																			
Had breast tenderness																																			
Had breast swelling or weight gain, or felt bloated																																			
Had headache																																			
Had joint or muscle pain																																			
At least one of the problems noted above caused reduced productivity at work, school, or home																																			
At least one of the problems noted above interfered with hobbies or social activities																																			
At least one of the problems noted above interfered with relationships with others																																			
Menstrual flow: H = heavy, M = medium, L = light or spotting (leave blank for no bleeding)																																			

NOTE: Patients should record the score for each item on each day using the following scale: 1 = not at all, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe, 6 = extreme. If during the mid-follicular phase (days 6 through 10) the patient has an average daily score greater than 3 for any symptom, an alternative diagnosis should be sought. Excused symptoms include appetite for obese patients, insomnia with good reasons, or pain from physical illness. The week before menses, the patient should score at least 4 for at least two days on five symptoms that correlate with premenstrual dysphoric disorder diagnostic criteria (Table 2). The week before menses, the patient should score at least 4 for at least two days on at least one impairment item. The patient must meet these criteria for two consecutive cycles or two out of three cycles. Clinical judgment should correlate with the assessment of daily ratings.

Information from Endicott J, Nee J, Harrison W. Daily Record of Severity of Problems (DRSP): reliability and validity. *Arch Womens Ment Health*. 2006;9(1):41-49.

Fig. 1 Daily Record of Severity of Problems for diagnosis of premenstrual dysphoric disorder

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carbonate either 500 mg bid or 1200 mg daily can reduce the symptoms of depression, appetite, and fatigue in women diagnosed with PMS [1]. Cognitive behavioral therapy (CBT) has been shown to improve functioning and depression scores for patients with PMS or PMDD. Lastly, mindfulness-based exercises or acceptance-based CBT may be helpful to reduce symptoms [1].

Amenorrhea and Oligomenorrhea

In order for a woman to have regular menstrual cycles, there must be a complex interaction between the hypothalamic pituitary axis, the ovaries, and the uterine outflow tract. A disruption at one of these sites can result in amenorrhea or oligomenorrhea. The workup for primary amenorrhea and secondary amenorrhea will be discussed separately; however, there is overlap in etiologies of these conditions.

Primary Amenorrhea

Primary amenorrhea is defined as a female who has not achieved menarche by age 16 or has not achieved menarche or developed secondary sex characteristics by age 14 [4]. A thorough history and physical examination should be completed paying particular attention to medications, weight gain or loss, breast and pubic hair development, galactorrhea, headaches, acne, hirsutism, and clitoromegaly.

Given that the most common cause for amenorrhea is pregnancy and lactation, the workup for all amenorrhea should begin with a pregnancy test. If negative, a prolactin, TSH, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) level should be checked. A pelvic ultrasound should also be completed to assess the outflow tract.

Outflow Tract Abnormalities

Outflow tract abnormalities account for roughly 20% of cases of primary amenorrhea [4]. Females with an imperforate hymen will have normal pubertal development but may experience cyclical pain during the onset of puberty. On exam, a bluish bulging mass can be seen at the entrance to the vagina which is called hematocolpos. Referral to a surgeon can reestablish normal menses [4].

Transverse vaginal septum develops in utero, and while location varies, it typically is high in the vaginal cavity [4]. Girls with a transverse vaginal septum have normal pubertal development and may begin to experience cyclical pelvic pain. On exam, a shortened blind vaginal pouch will be seen. Surgery is the definitive treatment for this condition.

Mullerian agenesis is an abnormal development of at least part of the mullerian tract which consists of the fallopian tubes, uterus, cervix, and upper two-thirds of the vagina. It causes 15% of primary amenorrhea and can be diagnosed with pelvic imaging [5]. Mullerian agenesis is associated with other renal and skeletal abnormalities; therefore, patients often require a multidisciplinary team [4].

Androgen insensitivity syndrome is a disorder in which a patient genetically has 46XY chromosomes and has testes that produce male levels of testosterone and anti-mullerian hormone; however, they have a defect in the androgen receptor. Patients develop female external genitalia; however, they do not develop the mullerian tract. Patients may present with inguinal hernias. Androgen insensitivity syndrome can be diagnosed through karyotyping and a testosterone level.

Gonadal Anomalies

Gonadal anomalies account for 30–40% of primary amenorrhea and should be suspected if there is an elevated FSH level [4]. Turner syndrome is classically a 45 XO chromosome genetic abnormality; however, it may also be the result of other X gene abnormalities. It is characterized by women of short stature, webbed neck, low-set ears, widely spaced nipples, short fourth metacarpals, and agenesis of the ovaries. Growth velocity may be slow starting as a toddler and continue into

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adolescence, and patients tend to have limited secondary sex characteristics. A specialist should manage these patients as replacing recombinant growth hormone, estrogen, and progesterone can help with normal growth and pubertal development. Patients may also have renal, cardiac, or ophthalmologic abnormalities [4]. Gonadal dysgenesis occurs in a woman who has 46XX chromosomes but does not develop functioning ovaries. Imaging will often identify streak gonads. Management should be completed through specialty referral. Swyer syndrome occurs in individuals with 46XY chromosomes who do not develop testes. They do develop normal internal and external female genitalia and require referral to subspecialist to remove testes due to high malignancy risk.

Hypothalamic and Pituitary Causes

Functional hypothalamic amenorrhea, medications, and hyperprolactinemia can cause primary amenorrhea but will be discussed in greater details under secondary amenorrhea. Constitutional delay is a delay in the onset of menarche and typically is found in patients with a family history of delayed puberty. This is a diagnosis of exclusion.

Secondary Amenorrhea

Secondary amenorrhea occurs when women who previously had regular menses cease to have menses for 3 months [5]. Oligomenorrhea is the lack of menstruation for longer than 35 days in adults and 45 days in adolescence [4, 5]. Adolescents may have irregular periods for 3 years following menarche.

For all women with amenorrhea, workup should begin with a b-hCG test to exclude pregnancy. If a thorough history and physical exam does not point to a specific cause, then checking a prolactin, thyroid-stimulating hormone (TSH), estradiol (E2), and follicle-stimulating hormone (FSH) level may provide additional diagnostic insight. Figure 2 outlines the diagnostic workup, and Table 2 outlines medications that can cause amenorrhea [6].

Hypothalamic Pituitary Axis

The hypothalamic pituitary axis plays an important role in controlling the menstrual cycle. When working up amenorrhea, abnormalities in serum prolactin, TSH, or low FSH levels would suggest the etiology is related to the hypothalamic pituitary axis.

Functional hypothalamic amenorrhea (FHA) is the disruption of ovulation caused by stress on the body. FHA can be caused by stressors including undernutrition, excessive exercise, emotional stress, or chronic disease. Classically, this is seen in the female athlete triad in which a woman has low-energy availability, menstrual dysfunction, and low bone mineral density. Labs usually reveal a low FSH and estradiol level. The patient should meet with a nutritionist if undernutrition or an underlying eating disorder is suspected. Menses generally resume when a patient returns to about 90% of ideal body weight [4]. Bone mineral density testing should be conducted in women who have been amenorrheic for 6 months or have a history of a stress fracture [5].

Hyperprolactinemia, diagnosed with an elevated serum prolactin level, often presents with infertility or amenorrhea. Patients may also complain of headaches, bilateral temporal visual field defects, or galactorrhea. Common causes of elevated prolactin levels could include pregnancy, lactation, pituitary adenomas, pituitary stalk disruptions, and medications [6]. Common medications that elevate prolactin include first-generation antipsychotics, methyldopa, and metoclopramide. An MRI of the pituitary is essential to look for masses in the hypothalamic pituitary areas of the brain. Pituitary adenomas >1 cm or adenomas that cause symptoms such as headaches or visual field defects should be referred to a specialist. Dopamine agonists may be used to treat elevated prolactin levels.

There are other disruptions to the hypothalamic-pituitary axis that can cause amenorrhea. Both hyperthyroid and hypothyroid disorders can disrupt menstrual cycles. Sheehan's syndrome, a condition in which the pituitary gland goes through ischemic necrosis due to blood loss, should be suspected in women who experienced a large postpartum hemorrhage. Cushing disease and

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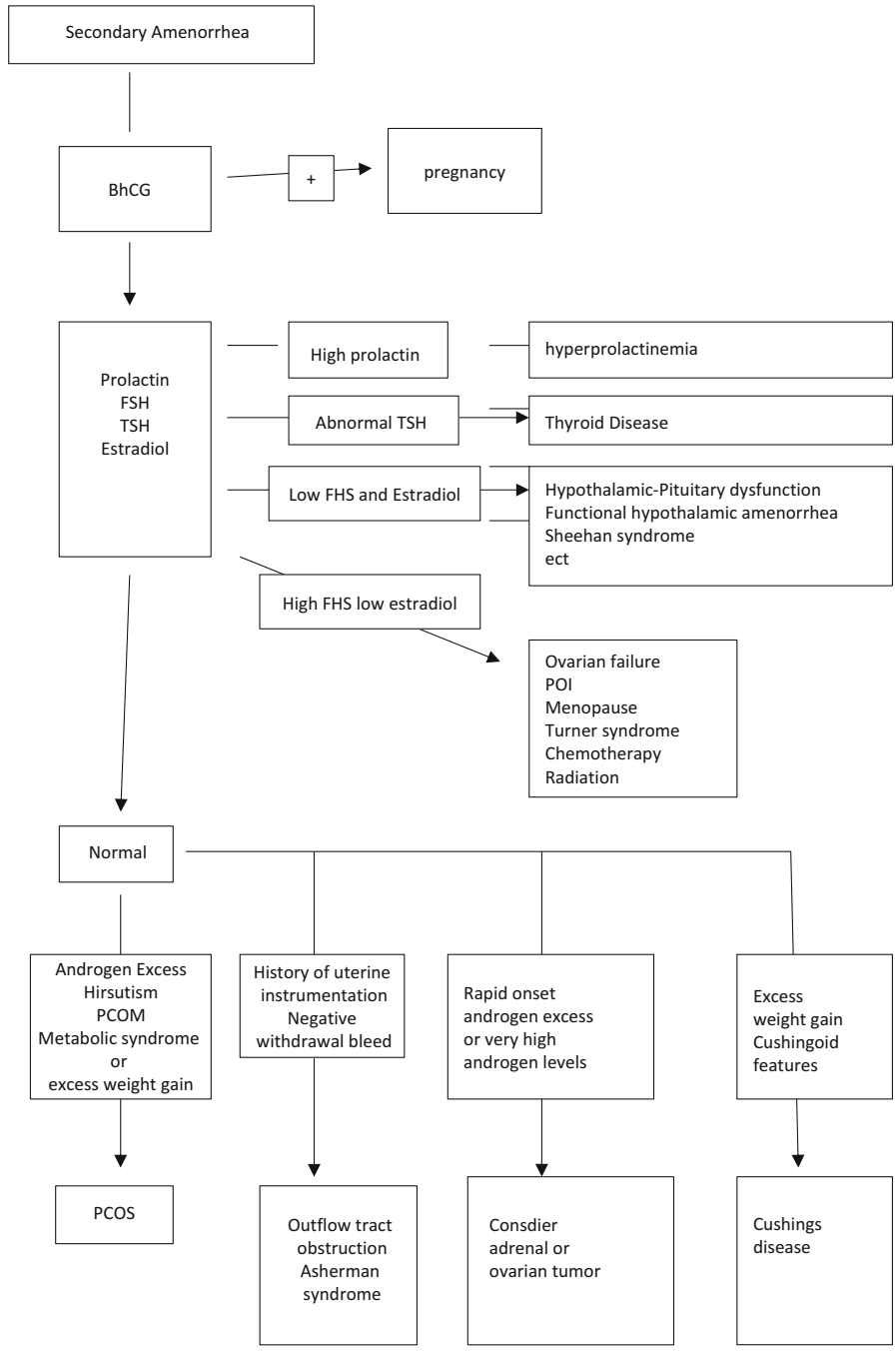


Fig. 2 Diagnostic workup for secondary amenorrhea

congenital adrenal hyperplasia are both rare causes of amenorrhea and should be considered if patients have exam findings concerning for elevated cortisol or elevated androgens [7].

Gonadal dysfunction would be suggested by elevated FSH levels and low estradiol levels. Primary ovarian insufficiency (POI), previously referred to as premature menopause, is the

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Table 2 Medications that cause amenorrhea [6]

GnRH suppression	Opioids
Hyperprolactinemia	Glucocorticoids Psychotropics GI motility agents Antihypertensives (verapamil, methyldopa)
Hypophysitis	CTLA-4 antibodies

development of ovarian insufficiency before the age 40. Women experience irregular menses or amenorrhea, hot flashes, and vaginal dryness. Women can be diagnosed with this condition by having two serum FSH levels in the menopausal range, 1 month apart [5]. Estrogen levels will be low but do not necessarily need to be checked. While most causes are idiopathic, Turner syndrome or its variants can cause POI, so karyotyping should be offered to women with POI. Chemotherapy, radiation, or autoimmune disease could also cause POI. Hormone replacement therapy may help with vasomotor symptoms to maintain healthy bone density and should be offered to patients until the natural age of menopause [5].

Outflow tract abnormalities are not a common cause of secondary amenorrhea but should be considered in high-risk populations. Intrauterine adhesions should be considered in women who have had intrauterine or endometrial procedures, particularly uterine curettage. Cervical stenosis should be considered in women who have had cervical procedures, radiation, or even vaginal birth [5]. It may be reasonable to try an estrogen/progestin withdrawal test to evaluate for bleeding. If no bleeding occurs, then an outflow tract abnormality is suggested. Pelvic ultrasound may be helpful in making the diagnosis; however, hysteroscopy may be required in order to diagnose an outflow tract obstruction.

Dysmenorrhea

Dysmenorrhea is defined as cramping abdominal pain occurring with menses [8]. Dysmenorrhea is considered to be primary dysmenorrhea if there is no pelvic pathology found to explain the symptoms. Primary dysmenorrhea often occurs within 6–12 months of menarche when ovulatory cycles are established. It is associated with normal volume menstrual flow and pain subsides after 2–3 days [9]. It is often prostaglandin-mediated. Dysmenorrhea is considered to be secondary dysmenorrhea if underlying pelvic pathology is identified. Often secondary dysmenorrhea occurs in women aged 20–30. Although many women do not find dysmenorrhea to be abnormal and do not seek medical treatment, it is the most common gynecologic condition reported among female adolescents and also affects 60–70% of adult women who menstruate [10, 11].

There are many important questions to ask about when taking a patient history including age of first menstruation, timing of dysmenorrhea onset, relation to menses and menstrual flow severity, description of the pain, sexual history, past medical and family history including chronic pain syndromes, presence of comorbid psychiatric disorders, associated gastrointestinal symptoms, and any previous treatment and response [9]. Patients, especially adolescents, may not be comfortable answering these questions. Upon initial presentation, an abdominal examination should be performed. A pelvic examination is not always necessary if there are not symptoms of a sexually transmitted infection or the patient has not been sexually active [10]. Laboratory evaluation and imaging are generally not helpful for the diagnosis of primary dysmenorrhea but may be helpful in the diagnosis of secondary dysmenorrhea. Table 3 delineates the possible differential diagnoses of dysmenorrhea.

Diagnosis of primary dysmenorrhea can be made from taking a detailed history and limited physical exam [10]. Secondary dysmenorrhea may be diagnosed after the history and physical

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Table 3 Differential diagnosis of dysmenorrhea [9, 10]

Primary dysmenorrhea	Secondary dysmenorrhea
	Endometriosis
	Adenomyosis
	Cervical stenosis
	Uterine leiomyomas
	Obstructions of the genital tract:
	Congenital malformations
	Pelvic adhesions
	Uterine polyps
	Pelvic inflammatory disease
	Irritable bowel syndrome or disease
	Ovarian cysts
	Cystitis
	Mood disorders
	Musculoskeletal pain

examination indicate an abnormal cause for the pain or subsequent abnormal laboratory evaluation or imaging or occurs [9].

Treatment of dysmenorrhea must be tailored to the underlying cause. Multiple pharmacologic interventions are effective for the treatment of primary dysmenorrhea in women of all ages. These pharmacologic therapies are targeted at reducing prostaglandin and leukotriene production to reduce overall pain perception. Nonsteroidal anti-inflammatory drugs (NSAIDS) are considered first line [12]. Table 4 is a summary of the frequently used NSAIDS.

Hormonal contraceptives are also considered to be another acceptable first-line option in addition to or in lieu of NSAIDS [10]. These include combined oral contraceptives in pill, patch, or ring form which all work to decrease the thickness of the endometrial lining [12]. Implantable contraceptive progestin rods, intramuscular medroxyprogesterone acetate, or intrauterine devices with levonorgestrel are also effective. Each method has associated risks and other benefits, so the decision to utilize a certain method should be tailored to each patient. Finally, many alternative and complementary therapies can be utilized for treatment of primary dysmenorrhea. These include physical activity which had the largest beneficial effect, acupressure which had a moderate effect, and heat therapy [8, 13]. Many medicinal plants including fennel, chamomile, and *Zataria multiflora* are reported to be effective as well; however, further studies are needed to clearly identify the risks and benefits of these treatments [14]. If primary dysmenorrhea does not improve within 3–6 months of starting treatment, family physicians should investigate for secondary causes.

Table 4 Recommended NSAIDs and doses for treatment of primary dysmenorrhea [10, 12]

Drug	Loading dose	Maintenance dose
Ibuprofen	800 mg	400–800 mg q 8 h PRN
Naproxen sodium (reduce doses by 50 mg if naproxen)	550 mg	220 mg–550 mg q 12 h PRN
Celecoxib	400 mg	20 mg q 12 h PRN
Mefenamic acid	500 mg	250-500 mg q 6–8 h PRN
Diclofenac potassium	100 mg	50 mg q 6–8 h PRN

If treatment for primary dysmenorrhea has failed or initial history and physical suggests a secondary cause, then imaging or surgical investigation for that cause should be pursued after appropriate referral. Endometriosis is the most common etiology of secondary dysmenorrhea and frequently responds to many of the same treatments utilized for primary dysmenorrhea; however, conservative surgical therapy and suppressive hormonal therapy are sometimes needed [12]. Continual patient education and multidisciplinary support can assist as well with both straightforward and complex cases to improve patient outcomes [10].

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Abnormal Uterine Bleeding

Abnormal uterine bleeding (AUB) had many different names prior to 2011 when the International Federation of Gynecology and Obstetrics (FIGO) issued guidance to update and standardize terminology [15]. Terms such as menorrhagia, metrorrhagia, hypo- or hypermenorrhea, polymenorrhea, and dysfunctional uterine bleeding are no longer recommended to be utilized [16]. FIGO recommends the use of the term AUB to describe any change in menstrual volume, frequency, or duration in nonpregnant females [16]. This condition is commonly experienced by approximately 1/3 of reproductive aged women, adds significantly to overall healthcare expenditures, and is well-addressed by family physicians [15]. Table 5 describes some normal features of menstruation.

Diagnosis of AUB can be made if conditions within the acronym PALM-COEIN are present as detailed in Fig. 3 [17]. AUB can be further subcategorized into regularly occurring ovulatory cycles with heavy menstrual bleeding (HMB) or irregularly occurring cycles with likely ovulatory dysfunction (AUB-O) [15].

Evaluation of the patient with AUB should always include a detailed history about menstrual cycle length, variability and volume, sexual history, past medical history of coagulation disorders, and inquiry about fatigue, pain, or mood changes [17]. Physical exam should assess the patient for signs of a bleeding disorder such as bruising or petechiae, sources of extrauterine bleeding such as cervical irritation or endocervical polyps, an enlarged uterus, signs of PCOS such as acne or hirsutism, signs of thyroid disease or galactorrhea, or obesity. Laboratory evaluation is limited but may include a completed blood count (CBC), pregnancy test, thyroid-stimulating level (TSH), prolactin level, sexually transmitted disease testing, cervical cancer screening, assessment for coagulopathy if physical exam is concerning, and possible endometrial sampling. Endometrial sampling is recommended in patients older than 45 or younger if additional risk factors are present such as PCOS, obesity, or failed medical management. Pelvic imaging is often ordered and includes transvaginal ultrasound as the initial test of choice, followed by hysteroscopy or other modality if further evaluation is required [18].

Treatment of AUB depends on the underlying cause. For women who have a structural cause identified, removal of the abnormality can alleviate symptoms. For women with a diagnosed endocrine condition such as hypothyroidism, obesity, or hyperprolactinemia, correction of the endocrine disorder can alter the hypothalamic pituitary axis (HPA) enough to enable the body to resume ovulation and correct the AUB. Correction of coagulopathy or discontinuation of anticoagulants can also alleviate bleeding.

Table 5 Normal menstrual cycle [17]

Frequency	24–38 days
Duration	4–8 days
Volume of blood loss	5–80 ml

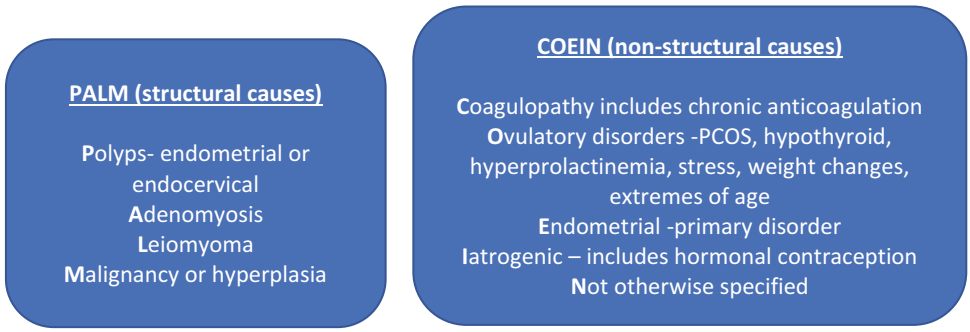


Fig. 3 PALM-COEIN

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Polycystic Ovarian Syndrome (PCOS)

PCOS is a common condition affecting somewhere between 5 and 20% of women during their reproductive years [19]. The Rotterdam Criteria define PCOS as a condition in which a woman has two of the following three findings: hyperandrogenism – either on clinical exam or found biochemically – oligo-ovulation or anovulation, or polycystic ovarian morphology (PCOM). Androgen excess often presents clinically as hirsutism (terminal hairs in a male-like pattern). Other signs of androgen excess could be acne or alopecia; however, these findings are less specific to androgen excess. While labs are not needed to confirm hyperandrogenism, free and total testosterone along with DHEAS can be checked if the exam is not conclusive [19]. It should be noted that hormonal birth control use in the last 3 months may alter these tests.

Ovarian dysfunction can present in different ways. Oligo-anovulation presents with menstrual cycles lasting longer than 35 days in length or having 10 or less cycles in a year. Women with ovulatory dysfunction may also present with frequent menstrual bleeding or even normal menstrual cycle duration without ovulation [19]. In these patients, a mid-luteal progesterone level or serial ultrasound monitoring can be used to assess ovulation [20]. PCOS may play a role in up to 80% of anovulatory infertility [20].

PCOM is typically found on ultrasound and is defined as having one or more ovary with a volume greater than 10 cm^3 or having an antral follicle count of 12 or greater [21].

Women with PCOS are at increased risk for metabolic dysfunction. Insulin resistance is common with PCOS patients being five to seven times more likely to develop type 2 diabetes mellitus [19]. They are also more likely to develop dyslipidemia. It is therefore recommended to screen for insulin resistance with a 2-h glucose tolerance test and lipid panel every 2–3 years. There are also higher rates of endometrial cancer, anxiety, and depression [19].

Women with PCOS present to their primary care providers with different primary concerns. Treatment should be therefore geared toward the patient's primary concern and treatment goals. In obese patients with PCOS, both calorie restriction and increased exercise are considered first-line treatment for helping with menstrual irregularities, infertility, insulin resistance, and hyperandrogenic symptoms [22].

Infertility is a common presenting symptom for patients with PCOS and accounts for roughly 80% of anovulatory infertility [20]. As stated above, diet and exercise are the first-line treatments for obese patients with infertility. Metformin alone may help establish ovulation in women with anovulatory PCOS and has obvious metabolic benefits. Ovulation induction with clomiphene citrate or letrozole are considered first-line medications for infertility; however, given the risk for multiple gestations, it should be only offered by experienced physicians [20]. If the patient desires to regulate menses but does not desire fertility, OCPs can be considered.

Hyperandrogenism can manifest as hirsutism, acne, and/or alopecia. OCPs have been shown to improve all these symptoms. Hirsutism may also be treated with cosmetic hair removal therapies, androgen receptor blockers, or finasteride [19]. Women suffering from acne can also be treated with topical antimicrobials or topical retinoids. Alopecia can be treated with topical minoxidil.

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Menopause

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Overview

Menopause is a natural occurrence that marks the end of woman's reproductive years. Menopause is often described as an absence of "periods." However, the process is most accurately defined as the permanent cessation of menses. Clinical menopause is recognized after 12 months of amenorrhea [1]. The normal transition period that occurs prior to menopause is known as perimenopause. This transition begins approximately 4 years prior to menopause and is a result of progressive decline in ovarian function. This transition leads to menstrual cycle disruption, with waxing and waning of ovarian function. During perimenopause and menopause, women will experience many symptoms that include hot flashes, vaginal dryness, as well as mood and sleep disturbances [2]. There are several treatment options, both hormonal and nonhormonal, to combat these unwanted symptoms. Since average life span has increased, most women can expect to live at least one third of their life in menopause. The menopausal transition (MT) presents women with unique health concerns related to disease prevention and quality of life.

The Female Reproductive Life Span and the Menopausal Transition

During fetal life, the ovary goes through a series of embryological changes that result in the development of a primordial follicle, which is described as an ovum surrounded by granulosa cells. At the time of birth, a female infant will have approximately two million primordial follicles [4]. By puberty, 400,000 primordial follicles remain. Throughout a woman's reproductive life, only 400–500 of the primordial follicles grow into mature follicles and ovulate. By menopause, few, if any, primordial follicles remain. As the number of primordial follicles approaches zero, the production of estrogen decreases. When production of estrogen falls below a critical value, there is no longer feedback inhibition on the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [4]. Eventually, estrogen production by the ovaries falls to zero and can no longer inhibit the production of FSH and LH. Instead, these gonadotropins are produced in large and continuous quantities. These hormonal changes ultimately lead to cessation of menses [3–5].

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Table 1 Stages of menopausal transition

Early perimenopause	Irregular menstrual cycles
	Ovulation may fail to occur
Late perimenopause	>60 days between menstrual cycles
	Skipped menstrual cycles
	Anovulatory cycles
	Episodes of amenorrhea
	Occurs within 1–3 years of FMP
	VMS may begin
Final menstrual period	Defined retrospectively
	Final period before 12 months of amenorrhea
Menopause	Cessation of menses for 12 months
Early postmenopause	2 years following the FMP
	VMS most likely to occur
Late postmenopause	5–8 years after the FMP
	Increased CV risk
	Altered bone metabolism
	Increasing symptoms of urogenital atrophy

FMP final menstrual period, *VMS* vasomotor symptoms

The hallmark of the MT (Table 1) is the change in the menstrual cycles, ultimately leading to cessation of periods. While many women progress through this transition without seeking medical care, a substantial number will have questions about the changes they experience. Women may consult their family physician for advice or reassurance during this time of transition.

Specifically, women may desire to know "what to expect" regarding the timeline of menopause and their menstrual cycles. Such questions can be challenging for the family physician to address, since the MT is characterized by irregularity. Predicting when menopause may occur has historically been difficult; however, in recent years there has been much interest in research directed toward better understanding and anticipating the MT.

The Stages of Reproductive Aging Workshop (STRAW) originally met in 2001 [6] to discuss the existing data on the MT. Since chronological age correlates poorly with menopausal changes, the goal of the workshop was to produce a staging system, analogous to the Tanner system for puberty, which could be used to objectively classify a woman's status in the MT. STRAW divided adult female life into three general phases: reproductive, menopausal transition, and postmenopause. These phases were further divided into seven stages, focused around the final menstrual period (FMP). The reproductive phase was divided into early (Stage 5), peak (Stage 4), and late (Stage 3a, 3b), The menopausal transition was divided into early (Stage 2) and late (Stage 1). Postmenopause, preceded by FMP, was divided into early (Stage +1a, +1b, +1c) and late (Stage +1). The resulting STRAW criteria have been well received and have guided further research in the field. The system was reviewed and updated in 2011 to reflect findings in the subsequent decade [7]. The updated staging system serves as the basis for the following discussion.

Stages of the Menopausal Transition

Late Reproductive Years

Even prior to entering the MT, women may notice changes in the flow or duration of their menses (e.g., "lighter" menses). Declining ovarian function results in decreased fertility. With a decrease in the number of developing follicles, there is a rise in FSH concentration. This is thought to be the result of decreased feedback inhibition of FSH and LH.

Early Menopause Transition

Change in the intermenstrual interval signals the beginning of the perimenopausal period. This change in bleeding patterns is the first symptom noticed by most women. The STRAW + 10 staging system [6, 7] objectively defines this stage as recurrent differences of ≥7 days in the length of consecutive cycles. For example, a woman experiences a cycle of 25 days followed by a cycle of 33 days. To meet the criteria, a similar discrepancy between consecutive cycle lengths should recur within ten cycles [7].

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Of course, many women will not present with such detailed records of their periods. The overall concept of cycle length irregularity, however, should be clinically discernible in most instances. The clinical significance of this stage is primarily that it allows physician and patient to be reasonably confident that the menopausal transition has begun. The length of this stage is quite variable.

In late perimenopause, estrogen production falls below a critical level when the number of primordial follicles approaches zero. Women begin to have skipped cycles, episodic amenorrhea, and an increasing frequency of anovulatory cycles. These irregular cycles are the result of dramatic variations in estradiol concentrations.

Late Menopausal Transition

When a woman experiences a gap of greater than 60 days between cycles, she can be said to have entered the "late" phase of MT. This objective landmark is typically easy to discern in the clinical setting and signifies that a woman is likely within 1–3 years of her FMP. This stage has additional clinical significance, as this is the time when many women will begin having menopausal symptoms such as hot flashes.

Final Menstrual Period and Early Postmenopause

The landmark of the FMP is identified in retrospect, when a woman has been amenorrheic for 12 months. The 2 years that follow the FMP are considered the early postmenopausal period and are notable for a high prevalence of vasomotor symptoms.

Late Postmenopause

Late postmenopause describes the phase where menopausal hormone changes have fully stabilized, approximately 5–8 years after the final menstrual period. At this point, many of the symptoms of the menopausal transition will have subsided, but the physiologic implications of the postmenopausal state persist, such as increased cardiovascular risk, altered bone metabolism, and urogenital atrophy [3, 6, 7, 8].

Laboratory Testing

Discerning a woman's status in the menopausal transition should be thought of as a clinical process guided by the menstrual cycle history. Although research efforts are beginning to better characterize the status of several markers (i.e., -follicle-stimulating hormone, estradiol, anti-Mullerian hormone) in the various stages of menopause, lab testing is not required for most women entering menopause at an appropriate age. The North American Menopause Society discourages the routine assessment of hormone levels [9]. However, a recent prospective from the Study of Women's Health Across the Nation (SWAN) showed that levels of anti-Mullerian hormone (AMH), along with age, may help estimate when a woman will undergo her FMP [10].

Epidemiology

The average onset of menopause is 51.4 years of age [13]. However, there is considerable variation among women. Approximately 5% of women undergo menopause after age 55, while in another 5%, onset will occur between 40 and 45 [5, 11]. This variation is thought to be due to several factors. Women with family members with early menopause are more likely to also experience early menopause [12]. According to STRAW, smokers both experience an earlier onset and a shorter MT duration. Black women experience a longer MT duration than White women. Lastly, those whose MT onset is earlier experience a longer MT duration [13].

Systemic Effects of Menopause

Menopause reflects a time of significant change for women. All the effects discussed below can have a substantial biopsychosocial impact, and

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they represent opportunities for the family physician to improve quality of life. The sequelae of menopause are widely underreported, and intentional screening should be considered part of high-quality care for perimenopausal and postmenopausal women.

Vasomotor Symptoms

One of the most common and well-known effects of menopause is the hot flash. Classically, these are "sudden episodes of intense heat that usually begin in the face or chest and spread throughout the body, accompanied by sweating and flushing that typically last 1–5 min" [14]. Physiologically, the symptoms largely result from peripheral vasodilation and inappropriate activation of heat loss mechanisms. Therefore, chills may follow the hot flash, as core body temperature is lowered [15]. Peri- and postmenopausal women are apparently predisposed to these reactions due to a narrowing of the thermoregulatory set zone in the hypothalamus [16]. This has been hypothesized as being related to the hormonal changes of menopause, but the exact mechanism remains unclear.

While estimates vary, a definite majority of women (up to 80%) will experience vasomotor symptoms (VMS) as they pass through menopause [7, 17]. Data on the duration of VMS suggest that the average length of symptoms is 7.4 years. SWAN identified four different subgroups of women in how they experienced VMS over the MT: (1) An early-onset group had VMS early in MT, which persisted after LMP but then declined; (2) later-onset group experienced VMS peaking during the FMP, persisting through and declining into postmenopause; (3) one group with few to none VMS during the MT; and (4) super flashers began VMS before FMP, and it persisted far into postmenopause [13]. It is important for the family physician to realize that both the experience and reporting of VMS will vary greatly between individuals.

On a larger scale, culture and ethnicity have a substantial effect on how women perceive their menopausal symptoms. SWAN showed Black women had the highest rate and longest duration of VMS and were most affected their VMS. Asian women reported the lowest rate of VMS, with Hispanic and White women landing between Black and Asian women. Lower socioeconomic status, less education, smoking, depression and anxiety, and a history of childhood abuse or neglect were associated with increased VMS. Thus, the family physician should make treatment recommendations on an individualized basis, taking the patient's unique experience into account.

Women who seek professional advice for their VMS should be counseled on lifestyle interventions and non-pharmacologic measures that may reduce their symptoms. These include smoking cessation, weight loss, stress reduction, lowering ambient room temperatures, and clothing choices [9, 14]. While supportive evidence for these interventions is limited, most are practical or bring other associated health benefits. The most effective treatment for VMS is hormonal therapy (HT). Other nonhormonal treatments that may reduce symptoms include paroxetine, venlafaxine, clonidine, gabapentin, and pregabalin [14]. Treatment will be discussed in more depth later in this chapter.

Sleep Disturbances

Perhaps one of the most challenging effects of menopause for the family physician to manage is sleep disturbances. In one large study, 38% of peri- and postmenopausal women reported sleep difficulty [18]. The menopausal transition has been shown in multiple studies to be strongly associated with sharp increases in the incidence of sleep disturbance and insomnia and increases over the MT [13]. However, there are numerous potential causes for sleep disruption in peri- and postmenopausal women, and in any given patient, several factors may be at play.

Vasomotor symptoms are a leading and clinically obvious cause for sleep disruption in perimenopause. However, even perimenopausal women without vasomotor symptoms have an increased prevalence of poor sleep [18]. Primary sleep disorders such as sleep-disordered breathing

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(SDB), restless leg syndrome, and periodic limb movement disorder all present with increased frequency in menopausal women [19]. Depression, anxiety, and other mood disorders may act as primary or secondary causes of insomnia. The overall health status of the woman must be taken into consideration, as worsening medical conditions can contribute to poor sleep. Medications should be reviewed, and sources of chronic and acute pain should be actively managed.

In summary, the approach to sleep disturbance in perimenopause must be highly individualized and involve careful attention to the patient's specific complaints. Standard sleep hygiene education should be provided. The patient's risk factors for sleep disturbance should be addressed. Several studies have assessed the effect of HT on sleep; however, findings have been mixed and difficult to compare due to the variety of study populations, HT formulations, and tools to evaluate sleep. A recent clinical trial of peri- and post-menopausal women with insomnia symptoms as well as daily hot flashes initially showed the effectiveness of cognitive behavioral therapy (CBT) in women with insomnia during the MT [19].

Urogenital Changes

Nearly all of the tissues of the lower genitourinary tract in females feature estrogen receptors, including the bladder, urethra, and pelvic floor musculature [15]. With the withdrawal of estrogen during menopause, these structures undergo several physiologic changes that can be clinically problematic for women. Previously known as vulvovaginal atrophy, this constellation of findings is now referred to as the *genitourinary syndrome of menopause* (GSM), in order to reflect the broad nature of effects that may be related to this transition.

It is thought that nearly half of women will experience genitourinary symptoms related to menopause [20]. The most commonly reported GSM symptoms are vaginal dryness and dyspareunia. In the SWAN cohort, vaginal dryness increased from 19% to 34% over the MT. The more advanced into the menopausal stage, the more likely vaginal dryness was reported. Women may experience dryness, irritation, and pain regardless of whether they are sexually active. Those who are sexually active may experience painful intercourse due to lack of lubrication and decreased elasticity of vaginal tissues. Loss of interest in or avoidance of sexual intercourse commonly results [13, 20]. Sexual functioning declines approximately 20 months prior to FMP and slows after FMP [13].

Urinary tract changes, such as urinary frequency, dysuria, and increased susceptibility to urinary tract infections (UTIs), are thought to be at least partially attributable to the hormonal changes of menopause [21]. Urinary incontinence (UI) was reported by 65% of the SWAN cohort at least once over a 9-year period of follow-up. Although UI is frequently reported, this is due to mid-life changes and not necessarily from menopause or decrease in estradiol [13].

The clinical approach includes screening for vaginal symptoms and dyspareunia, which women may be hesitant to voluntarily report. Objective findings on exam may include vaginal pallor and loss of rugae, as well as elevated vaginal pH (>5). It is important for the physician to consider and exclude other causes for the reported symptoms, such as vaginal infection, contact dermatitis, or lichen sclerosus [14, 21].

Once the diagnosis of GSM is established, women should be reassured of the possibility of treatment. Family physicians should be reminded that the symptoms of vulvovaginal atrophy are unlikely to improve without intervention [14]. For women with vaginal symptoms, local estrogen therapy is effective and has very few contraindications. Risk of endometrial stimulation remains a theoretical risk, so the lowest effective dose should be used, and any vaginal bleeding should be investigated [21]. Patients should be appropriately counseled on the unstudied safety profile of long-term use [14]. In women with additional menopausal symptoms, HT can be considered, as it is also effective for the symptoms of GSM.

Cognitive Changes

Many women perceive changes in their cognition during the MT. Memory loss or forgetfulness is

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one of the most common complaints, but women may also report a decreased ability to concentrate or multitask [9]. Studies investigating this phenomenon have validated some degree of correlation between subjective complaints and objective cognitive performance [31]. It is currently thought that minor declines can be attributable to the menopausal transition period but do not predict level of functioning later in life [9]. However, in any given patient, confounding factors may be in play. For example, subjective cognitive complaints are more common in the presence of mood symptoms and vasomotor symptoms.

Although several trials suggest modest cognitive benefit from HT, conflicting evidence exists [22]. The North American Menopause Society does not recommend HT for cognitive concerns or memory loss. Family physicians should focus efforts on optimizing other aspects of the patient's health by treating depression, reducing VMS, promoting sleep, encouraging physical activity, and avoiding medications that may affect cognition [9].

Mood Changes

The menopausal transition leading up to the final menstrual period appears to be a time of increased risk for symptoms of depression and anxiety. Depressive and anxiety symptoms have been reported more frequently during the late peri- and postmenopause than premenopause [13]. Stressful life events, increased financial strain, lower education, and being Hispanic were greater risks for depressive symptoms than menopausal status [13].

Although women may be more likely to present with non-affective complaints, family physicians should be alert to the possibility that depression and/or anxiety could be contributing to symptoms in the perimenopausal female. General symptoms of depression and anxiety should be carefully distinguished from actual mood disorders. The physician should assess the severity of the symptoms and their effect on functioning. Contributing biopsychosocial factors should be explored. Patients with mild depression or anxiety may benefit from cognitive behavioral therapy, whereas the addition of pharmacotherapy should be considered in patients with moderate to severe symptoms [9].

Skin and Hair Changes

The hormonal changes of menopause represent one of several factors driving the process of skin aging in postmenopausal women. General systemic aging, along with variables such as sunlight exposure and smoking, also plays a significant role. In general, postmenopausal women may notice thinning of the skin, increased skin laxity and wrinkles, and dryness of the skin [9, 23].

Women may note hair loss or hirsutism. Both changes may be related to a relative increase in androgens in comparison with estrogen in postmenopausal women. Common hair loss disorders include female pattern hair loss and telogen effluvium [9].

Interestingly, estrogen replacement therapy has been shown to improve various characteristics of both the skin and hair in postmenopausal women [9, 23]; however, treatment of skin or hair changes is not considered to be a primary indication for hormonal therapy.

Cardiovascular Disease

Menopause is a time of escalating cardiovascular (CV) risk in women. Over the MT, women will see unfavorable changes in lipid profiles, body fat distribution, metabolic syndrome risk, and vascular health [13]. It is well-known that premenopausal women have, on average, more favorable lipid profiles than men [15]. However, this advantage subsides at menopause, and cardiovascular disease (CVD) remains the number one cause of death in women [9, 15]. As the FMP approaches, the increased LDL levels are associated with a higher risk of plaque presence. While higher levels of HDL may not be protective [13]. The effect of hormonal changes on female lipid profiles led to a large-scale investigation of HT for reduction of CV risk, with the ultimate finding of inadequate benefit and unacceptable risk for routine use of HT in CVD prevention.

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Family physicians should be aware of the potential for abrupt changes in lipid profiles in the early postmenopausal period [9]. Aside from this, however, the prevention of cardiovascular disease in peri- and postmenopausal females does not differ substantially from other adult populations. Weight loss, exercise, and smoking cessation should be promoted. Blood pressure and cholesterol levels should be optimized. Diabetes mellitus should be screened for at appropriate intervals.

Osteopenia and Osteoporosis

Bone mineral density loss starts before the FMP, not after menopause. The estrogen deficiency of the MT promotes osteoclast activation, leading to a state in which bone reabsorption exceeds bone formation [24]. Following menopause, risk of fracture grows exponentially with age, and lifetime incidence of osteoporotic fractures is thought to be as high as 40% in Caucasian women [25].

In peri- or postmenopausal women, the evaluation begins with determining risk of fracture. Dual-energy x-ray absorptiometry (DEXA) objectively evaluates bone mineral density and is recommended for average-risk women at age 65. Earlier DEXA screening, however, should be considered in postmenopausal women thought to be at increased risk for osteoporosis [9]. Risk factors to consider include ethnicity (Caucasian and Asian women are at highest risk), low body weight, family history of osteoporosis and fractures, smoking, daily alcohol use, and use of high-risk medications such as systemic glucocorticoids. Some medical conditions can predispose to osteoporosis, such as rheumatoid arthritis or chronic kidney disease [25]. The patient's fall risk should be assessed, and women who have had a prior fragility fracture (fracture with fall from standing) are at particularly high risk for additional fractures. The Fracture Risk Assessment Tool (FRAX) developed by the World Health Organization incorporates many of the above risk factors and can be used to further guide clinical decisions.

Prevention efforts should include educating all women on the importance of adequate calcium and vitamin D intake and weight-bearing exercise. Supplemental calcium and vitamin D should be considered, as the average postmenopausal female receives approximately 500 mg less elemental calcium in her daily diet than recommended levels [25]. Osteoporosis is diagnosed by history of a fragility facture or by a bone mineral density (BMD) T-score <-2.5 at standard sites. In women with osteoporosis, as well as women with osteopenia and an elevated FRAX risk score, treatment should be considered [25]. Available options include bisphosphonates (Fosamax, Actonel, Reclast), selective estrogen receptor modulator (SERM) raloxifene (Evista), recombinant parathyroid hormone (Forteo), and calcitonin (Miacalcin). Estrogen replacement therapy has been shown to decrease fracture risk, but the benefit does not persist beyond discontinuation of therapy [25]. Estrogen replacement therapy is not currently FDA approved for treatment of osteoporosis.

Menopause Treatment

Overview

Most women manage the transition into menopause independently with approximately 10% of women seeking medical care. Symptoms of vaginal dryness, hot flashes, night sweats, and sleep disturbance most commonly prompt women to present to physicians [26]. Hormone therapy (HT) has been the mainstay treatment of menopausal symptoms for over 70 years. While HT is effective treatment for menopausal symptoms, some women may have underlying diseases that preclude use of hormones or wish to avoid risks associated with HT. Thus, there is expanding literature to explore alternative non-hormonal therapies (Table 5).

Hormone Therapy

Hormone therapy may include estrogen therapy alone (ET) or combined estrogen-progesterone therapy (EPT). Estrogen in combination with progesterone or alone is the most effective treatment of menopause-related vasomotor symptoms.

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Progesterone alone also reduces vasomotor symptoms but not as effectively as estrogen [27].

Indications

Appropriate indications for HT include vasomotor symptoms such as hot flashes, night sweats, and vaginal dryness. Topical hormone therapy may be sufficient for vaginal symptoms without systemic vasomotor symptoms. Until the publication of the Women's Health Initiative (WHI) in 2002 [28, 29], HT was widely prescribed for the prevention of cardiovascular disease, dementia, and osteoporosis; however, due to the increased health risks discovered by the WHI, prescription of HT for preventative measures ceased. Overall, the physician's decision to offer treatment of vasomotor symptoms may depend on a woman's perception of the severity of symptoms [26].

Effectiveness of Hormone Therapy

Hormone therapy has consistently shown to be effective for treating several menopause symptoms, particularly vasomotor symptoms. A meta-analysis of randomized controlled trials shows incidence of hot flashes with HT reduced by 75% compared to 50% reduction with placebo [26]. Stated another way, estrogen has been shown to reduce the frequency of hot flashes by approximately 2.5–3 hot flashes/day [29]. In addition to decreased risk of fractures, HT may offer a small to moderate improvement in sexual function by improving the vulvovaginal symptoms of vaginal dryness and atrophy [30]. Improvement in sexual function seems to occur via treatment of menopausal symptoms. Improvements in vasomotor symptoms and vaginal dryness can take, on average, 1–2 months after starting therapy [26].

Formulations

Hormone therapy is available in oral tablets, transdermal patches, topical gels and sprays, or intravaginal preparations (Table 2). Estrogen alone may be used in

Table 2 Hormone therapy formulations

Hormone class	Formulation	Medication brand name
Oral estrogen	Estradiol	Estrace
	Esterified estrogen	Menest
	Estropipate	Ortho-Est
	Conjugated equine estrogen (CEE)	Premarin
Oral progestin	Micronized progesterone	Crinone, Endometrin, Prometrium
	Medroxyprogesterone acetate	Provera
Progesterone-release IUD	Levonorgestrel	Mirena, Skyla, Kyleena, Liletta
Oral combination estrogen and progestin	CEE/ medroxyprogesterone	Prempro
	Estradiol/norgestimate	Prefest
	Estradiol/ norethindrone acetate	Activella, Amabelz, Mimvey
	Ethinyl estradiol/ norethindrone	FemHRT, Jevantique Lo, Jinteli
	Estradiol/drospirenone	Angeliq
Estrogen patch	Estradiol	Alora, Minivelle, Vivelle-dot, Climara, Menostar, Dotti
Estrogen-progestin patch	Estradiol/ norethindrone	CombiPatch
	Estradiol/ levonorgestrel	Climara Pro
Topical estrogen	Estradiol gel	Estrogel, Elestrin, Divigel
	Estradiol spray	EvaMist
Intravaginal estrogen ring	Estradiol: Systemic absorption for treatment of vasomotor symptoms	Femring
	Estradiol: Local absorption for treatment of vulvovaginal symptoms only	Estring
Intravaginal estrogen tablet	Estradiol	Vagifem, Yuvafem, Imvexxy
Intravaginal estrogen gel	Estradiol	Estrace
	CEE	Premarin

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women without a uterus. However, unopposed estrogen in women with a uterus increases the risk of endometrial hyperplasia [31], so progesterone must be added to estrogen in any woman with a uterus [30]. There is minimal systemic absorption of topical agents, so topical and intravaginal estrogen formulations are safe to use in women with a uterus without the addition of progesterone. Progestin-only formulations are available mainly in oral form; however, off-label use of levonorgestrel-releasing intrauterine devices (IUDs) has been shown to be both safe and effective [32]. Combination formulations are available as well.

Risks of Hormone Therapy

Known side effects of HT include nausea, breast tenderness, and irregular bleeding, especially early in menopause, as ovarian estrogen production fluctuates during this time [26, 27].

The Women's Health Initiative [26, 33, 34] unveiled many previously unknown risks associated with HT. Studies demonstrated that both estrogen therapy (ET) and estrogen-progesterone therapy (EPT) increased risk for stroke, venous thromboembolism (VTE), death by lung cancer, dementia, and gallbladder disease. Treatment with combined EPT also increased the risk of breast cancer and cardiovascular disease (CVD). Treatment with ET alone conversely was found to decrease breast cancer risk and not have an impact on CVD [30, 34].

There are many ways to numerically represent the increased risk posed by ET and EPT. Perhaps the most useful in counseling patients is by using the absolute risk (AR) over a defined time period (see Tables 3 and 4).

When using this data to counsel women on the risks and benefits of HT, there are caveats and nuances to keep in mind. Most data was collected in women with a mean age >60 years with only smaller groups of women in the perimenopausal or younger age group (age 50–59). This poses a major challenge for applying the data to clinical practice, since most women who seek hormone replacement therapy are in this younger age group. Furthermore, later subgroup analyses in the post-stoppage phases of the WHI-suggested CVD may be slightly reduced, rather than increased when hormone therapy (either ET or EPT) was initiated in women ages 50–59 [34]. However, this same age group also had an increase in breast cancer risk when started on combined HT [35]. Unfortunately, research on hormone replacement in this younger age group continues to be limited, even now 20 years after the WHI. Transdermal preparations may have a somewhat decreased risk of VTE, though further study is needed. Family physicians can expect the literature to continue to evolve in order to address specific factors such as age, proximity to menopause at the time of initiation, duration of HT therapy, and type of hormonal preparation.

Table 3 Risk of combined hormone therapy in postmenopausal women

Complication	Years of use	Absolute risk (AR)
Coronary event	After 1 year	4/1000
Venous thromboembolism	After 1 year	7/1000
Stroke	After 3 years	18/1000
Breast cancer	After 5.6 years	23/1000
Gallbladder disease	After 7 years	27/1000
Death from lung cancer	After 5.6 years (plus 2.4 years of follow-up)	9/1000
Dementia (>65 years, healthy)	After 4 years	18/1000

Adapted from Marjoribanks et al. [30]

Table 4 Risk of estrogen-only hormone therapy in peri- and postmenopausal women

Complication	Years of use	Absolute risk (AR)
Coronary event	After 1 year	4/1000
Venous thromboembolism	After 1–2 years	5/1000
	After 7 years	21/1000
Stroke	After 7 years	32/1000
Gallbladder disease	After 7 years	45/1000
Breast cancer	No significant increased risk	

Adapted from Marjoribanks et al. [30]

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Contraindications

Hormone therapy is contraindicated in women with a history of breast cancer, CVD, stroke, dementia, VTE, undiagnosed bleeding, or pregnancy.

Duration

Given the risks associated with HT, it is currently recommended to prescribe HT only in the lowest effective dose for the shortest possible time. Family physicians should regularly discuss with patients the ongoing need for therapy versus discontinuation. Short-term use of systemic HT is also clinically appropriate as hot flashes disappear within a few years of menopause for two thirds of women. Urogenital symptoms on the other hand are not self-limited, and frequently long-term therapy is needed. Topical and intravaginal therapy should be enough for urogenital symptoms [26]. Women with severe symptoms will need to balance the risk and benefits through informed decision-making with their physicians.

Monitoring

Regular review of continued need for HT by a woman and her physician is recommended. No specific interval is currently recommended, though every 3–6 months or at least annually is appropriate.

Intravaginal Hormonal Therapy

For women whose menopause symptoms are primarily vulvovaginal symptoms (e.g., atrophy, dryness, dyspareunia, etc.), the recommended treatment is intravaginal hormone therapy. While systemic hormone therapy will treat these symptoms, intravaginal therapy has significantly decreased risk for breast cancer, VTE, and stroke. Intravaginal HT is available as a cream, ring, or tablet (intravaginal pessary). These delivery systems have been shown to be equally effective at managing the symptoms of vaginal atrophy, with the main adverse side effect being the potential for thickening of the endometrial lining [36]. Caution should therefore be utilized in women with a history of endometrial hyperplasia or estrogen receptor-positive breast cancer. Vaginal moisturizers have similar efficacy to vaginal hormonal therapy and are thus excellent over-the-counter options for women who cannot or prefer not to use intravaginal hormone therapy [36]. Another nonhormonal option is the selective estrogen receptor modulator ospemifene, which is approved by the FDA specifically for moderate to severe vulvovaginal symptoms. As an oral tablet, it is an option for patients who prefer not to use an intravaginal treatment; however, it carries a risk of worsening vasomotor symptoms and an increased risk of VTE [37].

Bio-identical Hormone Therapy

There has been growing popularity of bio-identical hormone therapy (BHT), which technically refers to any hormone therapy that uses the same hormone produced endogenously (specifically 17β-estradiol). However, in lay communities this term is generally used to refer to hormones extracted from plants and modified to be structurally identical to endogenous hormones. These modified hormones are then compounded in variable combinations of estradiol, estrone, progesterone, testosterone, and DHEA by compounding pharmacies. These compounded formulations can take the form of pills, patches, gels, or suppositories. Many women have turned to BHT due to the assumption it is a more "natural" alternative to hormone therapy and thus safer than standardized HT. However; there is significant concern regarding the safety and effectiveness of BHT, as the compounding process is not standardized or regulated and the cost to patients is often quite high. A 2013 Cochrane Review analyzed 23 RCTs comparing efficacy for vasomotor symptoms and adverse events for BHT (unopposed 17 beta-estradiol) vs. placebo vs. conjugated equine estrogens. While there was low to moderate quality evidence that BHT improved vasomotor symptoms when compared to

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placebo, there was no significant difference in effectiveness when comparing BHT to conjugated equine estrogens. Results comparing the safety profile for BHT vs. HT were mixed, so the claim that BHT is safer than HT remains debatable [38].

Nonhormonal Therapy

Nonhormonal therapy may be an appropriate option for women with contraindications to hormonal therapy or those wishing to avoid risks associated with HT. A variety of treatment modalities have been investigated including antidepressants, clonidine, gabapentin/pregabalin, plant derivatives, acupuncture, hypnosis, and exercise.

Antidepressants

Some selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been shown to reduce hot flashes, possibly due to the role serotonin plays in mediating hot flashes. Most of the data comes from lower doses of antidepressants (i.e., venlafaxine 37.5–75 mg or paroxetine 12.5–25 mg) for relative short durations (4–12 weeks).

Paroxetine (Paxil): Studies [29] indicate on doses of paroxetine, 12–25 mg daily, women experienced fewer daily hot flashes than women taking placebo (3.2–3.3 versus 1.8 fewer episodes/day). A trial predominantly including women with breast cancer taking tamoxifen on 10–20 mg of paroxetine also had fewer daily hot flashes compared with placebo. Paroxetine was effective at both doses, but not surprisingly, women taking higher doses experienced more adverse effects.

Venlafaxine (Effexor): Additional investigations have shown that women taking venlafaxine at doses from 37.5 to 150 mg/day experienced decrease frequency of hot flashes (30–58% versus 19% compared to placebo). Effects were greater with higher doses, though most evidence is from doses of 37.5–75 mg daily. An RCT with a head-to-head trial comparing venlafaxine to estradiol showed slight superiority of estradiol compared to venlafaxine 75 mg daily. In this study, where mean hot flashes in the study group were 8/day, venlafaxine resulted in reduction to 5.5 daily episodes compared to 4.4 in the estradiol group [34].

Other SSRIs: Studies comparing fluoxetine (Prozac) and citalopram (Celexa) to placebo have failed to show a significant difference in vasomotor symptoms [29].

Alternative Pharmacological Therapy

Clonidine (Catapres): Meta-analysis shows that clonidine in doses of 0.05–0.15 mg daily may reduce hot flashes compared to placebo. Increased effect was seen at 8 weeks compared to 4 weeks of treatment [29]. Transdermal clonidine at 0.1 mg appears more effective than oral clonidine [26].

Gabapentin (Neurontin) and Pregabalin (Lyrica): A meta-analysis of studies comparing gabapentin and pregabalin compared to placebo showed a mean reduction of 1.62 hot flashes/day after 4 weeks and a mean reduction of 2.77 hot flashes/day after 12 weeks. While HT was still more effective than gabapentin/pregabalin, there was no significant difference between gabapentin/pregabalin and SSRIs [42].

Non-pharmacological Options

Plant and Natural Derivatives: Several naturally derived substances have been studied as an alternative for the treatment of menopause. Phytoestrogens are plant-derived products that have estrogenic activity. Soy isoflavones fit within this category and do show benefit for VMS and vaginal dryness [41] . Meta-analysis of red clover isoflavones, specifically Promensil and Rimostil, also showed possible slight benefit [29, 41]. Black cohosh, although widely utilized, has not been found to be beneficial [43]. Chinese herbal medicines are more challenging to study due to the varying combinations of herbs utilized, but thus far, meta-analyses have not shown a clear benefit. Several other natural products including evening primrose oil, dong quai, and ginseng have shown no benefit [26].

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Exercise: Historically there has been much debate regarding the connection between physical activity and menopause symptoms. While physical activity has been anecdotally reported as an acute trigger of VMS, it has also been proposed as a potential treatment for symptoms of menopause. A meta-analysis evaluating exercise as a trigger of hot flashes suggested that daily physical activity may increase the number of self-reported hot flashes (particularly in women with depression

Table 5 Systemic effects and treatment of menopausal symptoms

		Hormonal	Nonhormonal
Vasomotor symptoms (VMS)	Hot flash	ET, EPT (oral, transdermal)	SSRIs: Paroxetine (Paxil)
			SNRIs: Venlafaxine (Effexor)
			Clonidine (Catapres)
			Gabapentin (Neurontin)
			Pregabalin (Lyrica)
			Acupuncture
			Clinical hypnosis
Sleep[a]	Insomnia Poor quality of sleep		Sleep hygiene Cognitive behavioral therapy (CBT) Exercise Acupuncture
Urogenital	Vaginal dryness, irritation, pain Dyspareunia Urinary frequency Dysuria Increased susceptibility to UTIs	ET (transdermal, intravaginal)	Vaginal moisturizers Clomiphene
	Memory loss Forgetfulness Poor concentration Depressive mood Anxiety		Treat depression, offer CBT Reduce VMS Promote sleep Exercise, physical activity Avoiding medications that affect cognition
Skin and hair	Thinning of skin Increased skin laxity, wrinkles Dry skin Hair loss Hirsutism		Reassurance
Cardiovascular	Increased LDL level Decreased HDL level		Weight loss Exercise Smoking cessation Optimize blood pressure, cholesterol level Screen for diabetes mellitus
Bone	Osteopenia Osteoporosis		Calcium, vitamin D Bisphosphonates Selective estrogen receptor modulators Recombinant parathyroid hormone Calcitonin

[a]Consider treating other primary causes: hot flashes, depression, restless leg syndrome, obstructive sleep apnea, or periodic limb movement disorder; *ET* estrogen therapy, *EPT* estrogen-progesterone therapy, *SSRIs* selective serotonin reuptake inhibitors, *SNRIs* serotonin-norepinephrine reuptake inhibitors

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or anxiety), but not physiologic hot flashes, meaning women may perceive an increased number of hot flashes with exercise but there is no clear physiologic link for this observation [44]. Conversely, a Cochrane Review evaluating exercise as a treatment modality for vasomotor symptoms failed to show evidence of benefit [45]. Certainly for overall health, exercise remains a component of a healthy lifestyle, but given the current lack of evidence, it is difficult to make specific recommendations to women regarding the role of exercise for VMS.

Acupuncture: Multiple systematic reviews and meta-analyses have demonstrated that acupuncture improves VMS when compared with no treatment; however, there is no significant difference when compared with sham acupuncture [46]. Thus, clinicians may consider recommending acupuncture but should be clear about the limitations with patients.

Clinical Hypnosis: A single RCT compared clinical hypnosis to a control treatment showed a 74% decline in the frequency of hot flashes for the clinical hypnosis group compared to 17% decline for the control group. Similar differences were also noted for hot flash severity [47]. As these results have been demonstrated in only one RCT at this time, additional study will be beneficial to confirm results (Table 5).

Not all women will experience menopausal-related symptoms severe enough to warrant treatment; however, a substantial number will have questions about the changes they are experiencing and ways to maximize their health during the menopausal transition. Future evidence-based research will continue to help guide the family physician to successfully treat each woman in a holistic, individualized manner.

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Tumors of the Female Reproductive Organs

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Leiomyoma

General Principles

Definition/Background

Leiomyoma or fibroids arise from monoclonal proliferation or numerous copies of the same or very few cells [1] and are stimulated by estrogen and progesterone. They increase their growth rate during pregnancy and regress after menopause. They vary widely in size from a few millimeters to large masses filling the entire abdomen.

Epidemiology

Leiomyoma is the most common benign neoplasm of the female reproductive tract. It is present in 20–30% of women of reproductive age [2]. However, since many leiomyomata are asymptomatic, the true incidence is unknown. African-American women have a two- to threefold higher incidence than white women [3]. In addition, a systemic review by Stewart et al. [4] describe age, nulliparity, premenopausal state, hypertension, family history, time since parity, food additive, and soybean consumption to have a higher incidence.

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Classification

The easiest classification system is by anatomic location: (1) intramural, entirely within the walls of the uterus; (2) submucous, beneath the uterine lining; (3) subserous, which distorts the outer surface of the uterus; (4) intraligamentous; (5) parasitic, deriving its blood supply from another organ to which is has become attached; (6) pedunculated, attached to the uterus by a stalk; and (7) cervical.

Approach to the Patient

Risk factors have been identified which aid us in our approach to the patient. Fibroids are subject to hormonal stimuli. They arise with menarche and become inactive after menopause.

Diagnosis

History

Nonpregnant women with leiomyoma are often asymptomatic. The most common systems for which they seek treatment are abnormal bleeding and pelvic pain or pressure. If the myoma significantly distorts the uterine cavity, women may be infertile. Additionally, they may experience increased abdominal girth, urinary frequency, low back pain, and dyspareunia. There are also adverse pregnancy outcomes including malpresentation, dysfunctional labor, abnormal placentation, and abruption.

Physical Examination

The bimanual exam is the key physical exam procedure to identify a leiomyoma. A lobular, enlarged structure with a rubbery consistency may be found. Larger lesions can also be felt on abdominal exam.

Laboratory and Imaging

Anemia may be found as a result of abnormal uterine bleeding. Hydronephrosis may also be seen due to ureteral compression from the mass. Pelvic ultrasound remains the test of choice for diagnosis. Sonohysterogram or hysteroscopy can be used to confirm submucous leiomyomata.

Special Testing

MRI should be used sparingly due to its cost and the adequacy of other diagnostic imaging procedure. If there is an atypical lesion and concern for sarcoma is present, MRI would be appropriate. Endometrial biopsy can be performed if there is concern for endometrial cancer (see next section).

Differential Diagnosis

The most important diagnosis to be considered in the differential is leiomyosarcoma. It is rare but aggressive. However, of those rapidly growing leiomyoma (6 cm in 1 year), less than 0.1% of these are malignant. At surgery for women with presumed benign leiomyoma, the FDA estimates the prevalence of 0.277% for any uterine sarcoma and 0.134% for leiomyosarcoma [5]. Other diagnoses include solid ovarian tumors or uterine enlargement due to adenomyosis [1].

Treatment

Behavioral

Women with asymptomatic fibroids require no treatment.

Medications\Immunizations and Chemoprophylaxis

Women with abnormal uterine bleeding will often benefit from a trial of cyclic or continuous oral contraceptives or progestins. Prior to surgery, gonadotropin-releasing hormone (GnRH) agonists can decrease size and stop the bleeding. Long-term use of GnRH agonists has side effects such as osteoporosis. Mifepristone, an antiprogestin, may cause significant decrease in myoma size but may cause endometrial hyperplasia. Repeated intermittent use of ulipristal acetate, a selective P receptor modulator (SPRM), has shown efficacy in decreasing myoma size without causing concerning endometrial hyperplasia [6].

Referrals

For women whose symptoms continue despite treatment with medications, there are several

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surgical options. However, there are no well-conducted trials with US women comparing expectant management and various surgical procedures [1]. For women who wish to retain their fertility, myomectomy is generally offered. This procedure consists of removing the leiomyoma and then repairing the defect in the uterine wall. Myomectomy can be performed via laparotomy, laparoscopy, or hysteroscopy depending on the size, location, and number of lesions. There are several minimally invasive, uterus-sparing options. Radiofrequency volumetric thermal ablation (RFVTA) uses laparoscopic or transcervical routes using sonography guidance to place needle electrodes that use thermal energy to induce thermal fixation and coagulative necrosis in solid tumors, resulting in fibroid volume reduction and symptomatic relief [7, 8]. For women wishing to avoid surgery and who do not have future childbearing plans, uterine artery embolization can be used [9]. This procedure using angiography decreases blood flow to the uterus. This procedure has high (80–90%) success rates in decreasing blood flow and size and improving pelvic pressure [1]. However, it has been associated with surgical intervention within 2–5 years post-procedure [9]. For women who have completed childbearing and desire uterus-sparing options, magnetic resonance-guided focused ultrasound (MRgFUS) is also available; however, it is uncertain what the maximum myoma size threshold, candidate profile, and long-term outcomes for this method will be. MRgFUS is an outpatient procedure that involves noninvasive thermoablation that focuses multiple waves of ultrasound energy on a small area of tissue, thereby thermally destroying the tissue, with low short-term morbidity and rapid recovery [10]. Comparison of all three uterus-sparing modalities shows that RFVTA provides more significant fibroid and uterine volume reduction than uterine artery embolization or MRgFUS [10]. Finally, hysterectomy may be offered as a definitive procedure. The Agency for Healthcare Research and Quality (AHRQ) report concludes "The current state of the literature does not permit definitive conclusions about benefit, harm, or relative costs to help guide women's choices" [1].

Counseling

Fibroid tumors can be present in women with recurrent implantation failure, and appropriate counseling regarding their treatment would fall on the family physician [11]. Additionally, there are multiple factors related to successful hysteroscopic endometrial ablation including fibroids that could improve patient counseling.

Prevention

As mentioned above, nulliparity increases the risk of fibroids. Similarly, pregnancy is associated with a reduced risk of fibroids. Mifepristone, an antiprogestin, has been shown to decrease the size of leiomyomata by 50% [12]. Three WNT/beta-catenin pathway inhibitors, i.e., inhibitor of beta-catenin and TCF4 (ICAT), niclosamide, and XAV939, have been shown to block leiomyoma growth and proliferation [13]. Finally, a number of substances have been effective in the chemoprevention of fibroid tumors in quails [14, 15].

Endometrial Carcinoma

General Principles

Definition/Background

Endometrial cancer is the most common gynecological malignancy and the fourth most common cancer in women after breast, lung, and colorectal cancers. Incidence of endometrial carcinoma has increased by 1–2% annually, as has mortality [16]. Various theories to explain this increase included increasing life span and coexisting medical comorbidities in these women.

Epidemiology

The mean age at diagnosis is 60 years [17], and 90% of cases occur in women older than 50 years. 90% of cases occur in women older than 50 years, 20% of women have this diagnosis before menopause, and approximately 5% have disease before age 40 years [18]. Approximately 72% are stage I, 12% are stage II, 13% are stage III, and 3% are stage IV.

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Table 1 Classification of endometrial cancer

Type I	Type II	Familial
Low-grade	High-grade	Lynch
Minimal myometrial invasion	Deep myometrial invasion	
Arising in a background of hyperplasia	Serous or clear cell	
Perimenopausal Estrogen-related Younger age Obesity		

Classification

Endometrial cancer is commonly classified into three types (Table 1). The majority of women have Type I. With Type I, a genetic predisposition to obesity can increase one's risk of endometrial cancer. Type II occurs more commonly in older women, is more common in black women, and consists of higher-grade tumors. Genetic disease can represent up to 10% of cases, of which 5% are associated with Lynch syndrome, the hereditary nonpolyposis colorectal cancer syndrome.

Approach to the Patient

Risk factors have been identified, and these should be addressed including the possibility of a hereditary component. These risk factors, which will be discussed below, include obesity, reproductive, and menstrual factors.

Diagnosis

History

Abnormal uterine bleeding including postmenopausal, menorrhagia, or metrorrhagia is the most common presenting symptom for women with endometrial hyperplasia or carcinoma. Atypical glandular cells on cervical cytology should also be evaluated with colposcopy, endocervical curettage, and endometrial biopsy in women older than 35 or those with risk factors for endometrial cancer [19]. Nearly 70% of women with early-stage endometrial cancer are obese. Moreover, the relative risk for death for women with endometrial cancer increases with increasing BMI [20]. Continuous estrogen stimulation, both endogenous and exogenous, can alter the menstrual cycle resulting in anovulation. Anovulation results in continuous unopposed estrogen stimulation since there is no corpus luteum to produce progesterone. Obesity, through the peripheral conversion of androstenedione into estrone, results in increased endogenous estrogen and increases in the relative risk (RR) of endometrial cancer up to three times [21]. Estrogen-producing tumors, cirrhosis, unopposed estrogen therapy, and tamoxifen can also result in increased estrogen stimulation in the uterus. Although tamoxifen is an antiestrogen in breast tissue, it can have estrogenic activity in the endometrium [22]. Unopposed estrogen replacement during menopause increases the RR four to eight times, whereas combined estrogen and progesterone replacement therapy decreases the risk of endometrial cancer. Similarly, progestin-containing oral contraceptives or combined oral contraceptive pill decreases the risk of disease by nearly one-half. This increased risk associated with estrogen therapy continues until 2 or 3 years after cessation of therapy [23]. Nulliparity and diabetes are associated with a two- to threefold increase incidence of disease. Nulliparity is related to infertility rather than intentional prevention of pregnancy. Infertility is related to anovulation as discussed above as opposed to tubal factors. Although the incidence in white women is higher than in black women, stage for stage, black women have a less favorable prognosis. Regarding Type II disease, these patients account for 10% of cases, are not related to estrogen excess, tend to occur at an older age, and are poorly differentiated with serous or clear cell histology.

Physical Examination

In women with abnormal uterine bleeding and risk factors as mentioned above, concern for endometrial cancer must be pursued. Although a physical examination including bimanual may be important, the diagnosis is made based on histology. Endometrial biopsy is an office-based procedure for the family physician [24].

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Laboratory and Imaging

There are multiple modalities available to evaluate the endometrium. However, there is no recent ACOG Practice Bulletin to guide the clinician in choosing the modality. Endometrial biopsy (EMB) (with a piston catheter) is a simple procedure with good accuracy [25]. There have been a few retrospective studies comparing its accuracy to dilation and curettage (D&C) [26]. Although D&C was slightly better, it requires a visit to the operating room and anesthesia, whereas office EMB does not. Goldstein and colleagues who "were among the first Americans to publish on the high negative predictive value of thin distinct endometrial echo in postmenopausal patients with bleeding" [27] recommend beginning the evaluation with endovaginal ultrasound (EV-US). If the endometrial stripe is </4 mm in postmenopausal women or </5 mm in premenopausal women, no further diagnostic procedure is necessary (Fig. 1 in Goldstein [28]). Sweet et al. recommend EMB for women <35 years with recurrent anovulation and/or other risks for endometrial cancer. These risks include obese adolescents with 3 years of untreated anovulatory bleeding; women <35 years with chronic anovulation, diabetes, family history of colon cancer, infertility, nulliparity, obesity, or tamoxifen use; for women whose bleeding did not respond to medical therapy [29]. All women >/35 years with suspected anovulatory bleeding should have an EMB performed.

Special Testing

Saline infusion sonohysterography (SIS) can be used to evaluate the endometrial lining if transvaginal ultrasound does not provide adequate visualization. Sterile saline is instilled into the uterine cavity via a small catheter with ultrasound guidance. SIS can provide additional differentiation of focal lesions in addition to diffuse abnormalities such as endometrial hyperplasia. Newer techniques substitute gel for saline, which provides better technical results, and slightly increased sensitivity and specificity of detection of intrauterine lesions, compared to SIS [30]. Patients experience reduced discomfort because gel-instillation sonography uses a smaller amount of gel to distend the uterine cavity [31].

Differential Diagnosis

The differential diagnosis for abnormal uterine bleeding includes both malignancy as discussed above and benign causes. ACOG Practice Bulletin [32] reviews benign causes ▶ Chap. 105, "Selected Disorders of the Genitourinary System". The results of EMB show simple and complex hyperplasia both with and without atypia. The Gynecologic Oncology Group sought to validate the reproducibility of the referring institution's pathologic diagnosis of complex hyperplasia with atypia. They found the level of reproducibility to be poor [33]. Current recommendations are that women with both simple and complex hyperplasia without atypia and those with simple hyperplasia with atypia can be treated with progestins as the risk for endometrial carcinoma is low [21]. Cyclic medroxyprogesterone 10 mg daily for 14 days each month or continuous megestrol acetate 20–40 mg daily are both acceptable as is the placement of a progestin-releasing IUD. However, women with complex hyperplasia with atypia have >40% incidence of coexisting adenocarcinoma, and hysterectomy is the treatment of choice for these women. Alternatively, endometrial intraepithelial neoplasia is a new classification system designed to replace the hyperplasia terminology [34]. If this terminology were to be widely adopted by the pathology community, then this diagnosis may be more useful for clinical decisions than the current hyperplasia classification system.

Treatment

Behavioral

The most important behavioral intervention related to the prevention of endometrial cancer is weight loss, reviewed elsewhere in this text.

Medications\Immunizations and Chemoprophylaxis

As noted above, women with both simple and complex hyperplasia without atypia and those with simple hyperplasia with atypia can be treated with progestins. Cyclic medroxyprogesterone

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10 mg daily for 14 days each month or continuous megestrol acetate 20–40 mg daily are both acceptable as is the placement of a progestin-releasing IUD. These women should have a repeat EMB in 3–6 months and referral to a gynecologist if the hyperplasia persists.

Referrals

All women with complex hyperplasia with atypia and those with adenocarcinoma need referral to a gynecologist or gynecologic oncologist, respectively.

Cervical Cancer

General Principles

Definition/Background

Invasive cervical cancer is the third most common gynecologic cancer among women in the United States [35]. There are two histological types of cervical cancer, adenocarcinoma and squamous cell carcinoma. The human papilloma virus (HPV) is detected in 99.7% of all cervical cancer [36], with HPV types 16 and 18 accounting for 70% of those cases [37]. The epidemiology, risk factors, diagnosis, screening, prevention, and treatment of cervical cancer will be reviewed here.

Epidemiology

Worldwide, cervical cancer is the third most common malignancy [37]. There were 13,170 new cases of cervical cancer and 4,250 cervical cancer-related deaths in the United States in 2019. Cervical cancer estimates are higher for particular racial and ethnic groups with incidence and mortality being higher in African-American, American Indian, and Alaskan Native women than white and Asian women in the United States. Estimates are also higher for Hispanic women than non-Hispanic women. The incidence is highest in Hispanics/Latinos at 9.3 per 100,000 and mortality highest in African-Americans with 3.5 deaths per 100,000 cases [38]. There has been an overall decrease of deaths by 30.66% from 1990 to 2007 and a 50% reduction in incidence over 30 years from 1975 to 2006 [39]. From 2007 to 2016, death rates have fallen about 0.7% each year [38].

Risk Factors

Epidemiological risk factors for cervical cancer are well documented. Some are modifiable, which speaks to the importance of patient education and awareness for increased risk. Human papilloma virus (HPV) infection is a well-established risk factor for cervical cancer. Most risk factors are linked with the increased risk of acquiring HPV. These risks include early onset of sexual activity, multiple sexual partners, history of sexually transmitted infections, sexual partner (s) infected with HPV, history of vulvar or vaginal intraepithelial neoplasia or cancer, and immunosuppression [40]. Another major risk factor associated with cervical cancer is smoking [41]. In utero diethylstilbestrol (DES), previous treatment of high-grade precancerous lesions and history of cervical cancer are also risk factors [42]. Although unclear, socioeconomic status, three or more full-term births, young age at first delivery (less than 20 years of age), and oral contraceptive use may also increase risk. Other high-risk groups include refugees and women who have immigrated to the United States from countries where cervical cancer screening is not routinely performed and women without access to health care [43] (Table 2).

Classification

Cervical cancer is classified as squamous cell carcinoma, adenocarcinoma, adenosquamous or mixed carcinomas, and small cell carcinoma. Squamous cell carcinoma accounts for approximately 90% of cervical cancers, adenocarcinoma

Table 2 Risk factors for cervical cancer [44]

Risk factor	Relative risk
Menarche to first coitus <1 year	26.4
Age at first coitus <16 years	16.1
More than three sexual partners before age 20	10.2
Never having a pap smear	8.0
Cigarette smoking >20 years	4.0
History of genital warts	2

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comprises the other 10% with adenosquamous, and small cell carcinomas are rare.

Diagnosis

As described in Moore's approach to cancer management, there are four steps involved: (1) Establish the diagnosis. (2) Define the extent of disease. (3) Determine and implement treatment. (4) Follow the patient for evidence of recurrence and/or treatment-related complications [45].

History

Early cervical cancer may be asymptomatic. Common symptoms of cervical cancer include irregular vaginal bleeding, heavy vaginal bleeding, dyspareunia, and postcoital bleeding [40]. Unusual vaginal discharge may be described and can be purulent, malodorous, bloody, watery, or mucinous [46]. Taking a careful history and proper diagnostic testing must be performed as to not mistake these symptoms for cervicitis or vaginitis. Advanced cervical cancer may lead to lower back or pelvic pain and bowel and urinary symptoms. Advanced disease that has invaded nearby structures may lead to vaginal fistula formation (causing vaginal passage of urine or stool), hematuria, or hematochezia. Advanced disease may also present with deep venous thrombosis, ureteral obstruction, and lower leg edema from invasive spread [40].

Physical Examination

When a woman presents with a history or symptoms concerning for cervical cancer, a physical exam should be performed. A pelvic examination including a speculum exam for direct visualization of the cervix is paramount. Palpation of the groin and supraclavicular lymph nodes is part of a complete exam. Visualization of the cervix may demonstrate a normal appearing cervix, visible cervical lesion, or large tumor(s). All lesions that are friable, raised, or appear to be condyloma should be biopsied. Staging examinations also include a pelvic examination with the addition of a rectovaginal exam and calculation of tumor size and parametrial and vaginal involvement.

Laboratory and Imaging

Cervical cytology should be performed for all women when cervical cancer is suspected. HPV co-testing is done in screening but is not used for the diagnosis of cervical cancer when a woman presents with symptoms or has a visible lesion. In the initial evaluation of women with suspected cervical cancer, a cervical biopsy may be performed or may be part of a staging procedure. Imaging (MRI) is typically not used for the diagnosis of cervical cancer, but is useful in staging and evaluation of women with a known malignancy [47].

Differential Diagnosis

The differential diagnosis of cervical cancer includes mimics of the common symptoms of cervical cancer including irregular or heavy vaginal bleeding, postcoital bleeding, and abnormal vaginal discharge. Cervicitis, structural abnormalities, uterine leiomyoma, endometrial polyps, adenomyosis, endometritis, and pelvic inflammatory disease may all cause abnormal uterine bleeding. Visible cervical lesions including nabothian cysts, mesonephric cysts, cervical ectropion, ulcers from STIs, reactive glandular changes, and endometriosis are also on the differential for cervical cancer.

Treatment

Staging

Staging is performed before the proper treatment is chosen. Staging of cervical carcinoma is based on clinical staging as defined by the system set forth by the International Federation of Gynecology [45] and considers the size and invasion of the lesion with stage IV being the most advanced disease [48, 49]. Cervical carcinoma can metastasize hematogenously, lymphatically, or directly to adjacent tissues. A lymph node evaluation must be performed to ascertain involvement as this information could affect treatment options and planning. The most common sites of distant metastasis include the pelvic, aortic, and mediastinal lymph nodes, lungs, liver, and skeleton [50].

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Treatment Options

Treatment options depend on staging including localized disease, locally advanced disease, and metastatic or recurrent. Treatment options vary and may include surgery, radiation, brachytherapy, and chemotherapy. The patient's comorbidities, fertility desires, and risk of recurrence should also be considered when determining which treatment is best [50].

Referrals

Patients with diagnosed cervical cancer need referral to a gynecologist oncologist as soon as the diagnosis is made. Referring to other oncology services, such as patient centered support groups, and to a social worker (to help with financial questions or concerns, additional community resources, and support) is helpful for the patient as they are coping with a new diagnosis or recurrent cervical cancer.

Screening

In 2018, the US Preventive Services Task Force (USPSTF) updated the 2012 statement on screening for cervical cancer [51]. These recommendations are similar to the ACS/ASCCP/ASCP and ACOG current guidelines [52].

These recommendations are for women who have a cervix and do not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion, cervical cancer, and exposure to diethylstilbestrol or women who are immunocompromised [42]. These recommendations apply regardless of the patient's sexual history [52]. Screening recommendations from the USPSTF including techniques, initiation, frequency, and management of abnormal screening results will be discussed here.

Techniques

Cervical cytology screening techniques include the more common liquid-based cytology and the conventional Papanicolaou (Pap) smears. Both are considered acceptable forms of screening by the ACOG [43]. These are discussed collectively as cervical cytology. Available HPV DNA tests include HPV high risk, HPV 16 and 18 DNA, and Hybrid Capture 2 HPV DNA. Testing for low-risk HPV types is not useful.

Initiation and Frequency

Cervical cancer screening with a pap smear is recommended to start at age 21 years based on guidelines set forth by the US Preventive Services Task Force in 2018, ACS/ASCCP/ASCP, and ACOG [42, 43, 52]. Annual screening is not recommended for all women. Cytology results from previous pap smears, age, immune status, and previous HPV testing influence recommended screening intervals [51].

The ACS identifies groups that may require more frequent testing including individuals with a history of cervical cancer, history of a high-grade precancerous lesion, HIV, immunosuppression, and in utero exposure to DES [52]. For HIV patients, ACOG recommends a screening pap smear twice in the first year after diagnosis and then annually thereafter [53].

All guidelines mentioned above for cervical cancer screening recommend cytology alone for screening every 3 years for woman ages 21–29 years of age. Screening of women between the ages of 20 and 24 has been shown to have no impact on rates of invasive cancer up to age 30 [54]. For women between the ages of 30 and 65 years, cytology alone can be performed every 3 years according to the USPSTF guidelines [42]. The USPSTF states that in this age group, women who wish to extend screening to every 5 years may do HPV testing alone or cytology with HPV co-testing but that this may lead to additional testing. The ASC/ASCCP/ASCP and ACOG guidelines recommend screening in combination with cytology and HPV testing every 5 years in women ages 30–65 [55].

The USPSTF recommends stopping cervical cancer screening for women older than age 65 with adequate prior screening, not otherwise at risk for cervical cancer [42]. This recommendation defines adequate screening as two consecutive cytology negative pap smears with negative HPV co-testing in the 10 years prior to stopping screening (with the last test within 5 years) or three consecutive negative cytology

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tests. In addition, women who have had a total hysterectomy and have no history of CIN 1 or 2 or cervical cancer also do not need continued screening. Women who have had a high-grade precancerous lesion should continue testing for 20 years after management of the lesion [52].

The Bethesda system from 2001 is a standardized framework for laboratory reports for cervical cytology. The report attests to specimen adequacy and gives a descriptive diagnosis. There have been three revisions since 1988 [56]. In 2012, experts from national and international health organizations, federal agencies, and professional societies convened to revise the 2006 American Society for Colposcopy and Cervical Pathology Consensus Guidelines. From this meeting arose new evidence-based consensus guidelines for managing women with abnormal cervical cancer screenings tests, CIN, and adenocarcinoma in situ (AIS) [57]. The new longer screening intervals recommended by ASCCP, ACOG, and USPSTF were incorporated into these guidelines. These guidelines are the standard of care for managing abnormal cervical cancer screening tests. They can be found on the ASCCP website (http://www.asccp.org). The 2014 Bethesda System Update is included in the 2015 publication of *The Bethesda System for Reporting Cervical Cytology: Definitions, Criteria, and Explanatory Notes* [56].

Colposcopy

Colposcopy is used to visualize mucosal abnormalities of the cervix that may be suspicious and require biopsy. A colposcope is a low-power magnification device that permits the visualization of abnormalities of the cervix that are consistent with CIN or invasive cancer. During colposcopy, the cervix is washed with a solution of acetic acid which turns areas of the cervix white that have high nucleic acid. Biopsies are then procured and sent for histopathology. Results from colposcopy dictate the next steps in management. The 2015 ASCCP guidelines guide practitioners through the standards of care based on histopathology results. These guidelines can be found on the ASCCP website.

Prevention

Primary Prevention

Behavioral intervention to modify known risk factors for cervical cancer may modify the incidence of cervical cancer. Practitioners can use techniques such as motivational interviewing to help patients decide which risk factors they would like to modify. Primary prevention such as quitting smoking, condom use, using contraception methods other than oral contraceptive pills, and limiting the number of sexual partners can modify an individual's risk.

Medications/Immunizations and Chemoprophylaxis

HPV is associated with development of anogenital cancers including cervical, vaginal, vulvar, and anal. HPV is divided into two classes: non-oncogenic (low-risk) and oncogenic (high-risk). Low-risk HPV genotypes including 6 and 11 are associated with condyloma and mild dysplastic changes that typically do not progress. High-risk HPV types including 16, 18, 31, 33, 35, 45, 52, and 58 are associated with moderate (CIN 2) and severe dysplasia (CIN 3) [37, 50]. As previously noted, the high-risk types are seen in most cervical cancers. Only a small percentage of women with HPV will develop cervical cancer or abnormalities, as HPV alone is usually necessary but not a sufficient precursor for the development of squamous cell carcinoma [43].

Vaccination against the genotypes known to be the etiology of most cervical cancers is given with the intent to reduce the incidence of anogenital cancers. The Food and Drug Administration has approved three vaccines for the prevention of HPV infection. The bivalent three-dose vaccine, Cervarix, is approved for females ages 9–25 years to prevent cervical cancer, CIN1, CIN 2, and adenocarcinoma in situ caused by oncogenic HPV genotypes 16 and 18. The quadrivalent three-dose vaccine is approved for females and males age 9–26 years and protects against HPV genotypes 6, 11, 16, and 18. It is indicated to prevent cancers and intraepithelial neoplasias of the cervix, anus, vulva, vagina, and genital warts associated with the aforementioned genotypes [58]. The

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newest vaccine, GARDASIL 9, is a nine-valent vaccine against HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58. It is approved for males and females. There are two recommended vaccine schedules. The first schedule includes two doses, the first dose before age 15 and the second dose 6–12 months after the first dose. The second schedule includes three doses, the first dose after age 15, the second dose 1–2 months after the first dose, and the third dose 6 months after the first dose. The GARDASIL 9 vaccine has the same indications as the quadrivalent vaccine but covers more HPV genotypes [50].

The American Academy of Pediatrics (AAP) and CDC recommend that both boys and girls get routine HPV vaccinations if they are between 11 and 26 years old. Practitioners can administer vaccinations to patients as early as age 9. For those under 15, the two-dose GARDASIL 9 vaccine is recommended. For those over age 15 or with immune deficiencies, the three-dose GARDASIL 9 vaccine is recommended [59]. The CDC recommends that adults between ages 27 and 45 consult their physicians to determine their risk of new HPV infections before getting vaccinated [50].

Long-term effects of HPV vaccination on prevention of cervical cancer and CIN 2 and 3 are unknown; however, studies are currently being done [60]. Since there is no long-term data to help deduce how vaccination may alter the need for screening with cytology or cytology with HPV co-testing and the HPV vaccines do not include all high risk HPV genotypes, women who have been vaccinated against high-risk HPV infection should continue to be screened according to the USPSTF guidelines [42].

Secondary Prevention

The pap smear is a screening tool used to detect changes in cervical cells. In 2015, the American Society for Colposcopy and Cervical Pathology (ASCCP) with partnered organizations revised their 2006 consensus guidelines, recommending management of women with cytological abnormalities. The 2014 Bethesda System terminology [56] is used for cytological classification. Using the algorithms set forth in the ASCCP 2015 guidelines, practitioners are guided through the possible outcomes of cervical cytology from a pap smear based on results, age, and history of previous pap smear results. Within the guidelines, HPV testing only refers to high-risk, oncogenic HPV types only. The 2015 ASCCP guidelines can be accessed at http://www.asccp.org/guidelines.

Ovarian Cancer

General Principles

Definition/Background

Ovarian cancer is the second most common gynecologic malignancy and is the leading cause of death from gynecologic malignancies in the United States [35]. The majority of ovarian malignancies, approximately 90%, are derived from epithelial cells [61]. Epithelial carcinoma of the ovaries, fallopian tubes, and peritoneum are clinically similar, and there are five main subtypes which include high-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma. The other types of ovarian malignancies include germ cell tumors and sex cord-stromal tumors.

Epidemiology

In 2018, there were 22,240 expected cases of ovarian cancer, with an expected 14,070 deaths in the United States [62]. It is the fifth leading cause of death of women in the United States [62]. Based on data from 2014 to 2016, approximately 1.3% of women will be diagnosed with ovarian cancer during their lifetime, and in 2016, the number of women living with ovarian cancer in the United States was 229,875 [63]. Rates for new ovarian cancer in the United States have been falling on average 2.3% for the past 10 years [64]. Only 14.9% of ovarian cancers are diagnosed at stage I, and the 5-year survival rate for ovarian cancer found at stage I is 92.4% [63]. The 5-year survival rate declines with increasing stage, and the overall 5-year survival rate across all stages is 47.6% [64].

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Risk Factors

The pathogenic mechanisms for ovarian cancer have yet to be explained. Currently, there are two predominant hypotheses – incessant ovulation and exposure to gonadotropins. The theory of incessant ovulation was born out of data which demonstrated that women with history of pregnancy, lactation, or contraceptive use have a lower incidence of epithelial ovarian cancer. The gonadotropin exposure hypothesis is less supported by data and comes from the observation that experimentally induced ovarian tumors have gonadotropin receptors. Others have suggested that reproductive hormones [65] or chronic inflammation [66] may play a role in ovarian carcinogenesis. Although these separate theories may relate to the heterogeneity of epithelial ovarian cancers, none of them are able to fully explain the pathogenic mechanisms [61].

Family History/Familial Ovarian Cancer Syndromes

The strongest risk factor for ovarian cancer is family history. It is important to differentiate women who have a history of an isolated family member with ovarian cancer and those that may have a rare familial ovarian cancer syndrome from germline mutations including BRCA1 or BRCA2 mutations or Lynch syndrome. Women with Ashkenazi Jewish heritage with a single family member with breast cancer before age 50 or ovarian cancer are also considered to have a high-risk family history.

Reproductive/Hormonal Factors

Overall, the data seems to support the hypothesis of incessant ovulation as a risk for ovarian cancer. Women who are multiparous or who take oral contraceptives have a decreased risk of epithelial ovarian cancer. Women with early menarche and late menopause may be at an increased risk. Women with infertility may also be at an increased risk; however, data is currently inconclusive. The Women's Health Initiative found no increased risk for women on combined estrogen-progestin therapy compared with placebo [67]. Breastfeeding is thought to be protective against epithelial ovarian cancer, but further studies are warranted [68].

Environmental

Environmental risk factors include cigarette smoking and exposure to asbestos, a known carcinogen. Increased risk with perineal use of talcum powder is controversial. The association may be explained by the similar structure between talcum powder and asbestos, and that decades before, some talcum powder was contaminated with asbestos. Smoking increases the risk of mucinous ovarian cancer, with increasing amount of smoking leading to increased risk [69].

Other

Obesity seems to increase the risk of ovarian cancer [70]. Risk also increases with age. Taller individuals are also thought to be at an increased risk of ovarian cancer, with an 8% risk increase per 5 cm height [71].

Diagnosis

History

Ovarian cancer is typically diagnosed at a late stage. However there is evidence demonstrating that women will present with symptoms, even in early stages, that may get overlooked [72, 73]. Ovarian cancer can cause a myriad of symptoms, and distinguishing these symptoms from symptoms that normally occur in women or those that may be caused by a different medical disorder is problematic. Majority of women with epithelial ovarian cancer will present with a pelvic or abdominal symptoms prior to their diagnosis. Abdominal pain or discomfort and abdominal bloating or swelling are the most common symptoms. Patients may note urinary frequency, early satiety, and back pain. What may help distinguish these symptoms from other medical conditions is their more frequent and severe nature in those with ovarian cancer.

Physical Exam

If a pelvic mass is suspected or woman has symptoms suggestive of an epithelial ovarian cancer, a physical exam is warranted and should include an abdominal, pelvic, rectovaginal, and lymph node exam. A lymph node exam should include evaluation of groin and supraclavicular lymph nodes. If

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a physical exam is suspicious for a mass or other secondary symptoms of ovarian cancer such as ascites are found, further investigation is warranted with labs and imaging.

Laboratory and Imaging

If a physical exam and history is concerning for possible ovarian cancer, a Ca 125 tumor marker and abdominal and transvaginal ultrasound should be obtained. If the physical exam is benign, waiting 2 weeks to see if symptoms resolve prior to ordering pelvic ultrasound is reasonable.

Differential Diagnosis

The differential diagnosis for epithelial ovarian carcinoma and tubal and peritoneal carcinoma is variable depending on the presentation of the patient. Patients can have a myriad of symptoms though typically these will be urologic or gastrointestinal in nature. In women who do not have an adnexal mass on exam and imaging, workup for other causes of their symptoms is warranted and may be done simultaneously.

Staging/Treatment

Referrals

Ovarian, fallopian tube, and peritoneal cancers may require surgery for diagnosis. Primary care providers should refer to a gynecologist oncologist for the staging of these cancers and their surgical management.

Medications/Chemoprophylaxis

After diagnosis, a gynecologist oncologist will make recommendations based on the type and stage of the ovarian cancer. The main treatments for ovarian cancer include surgery, chemotherapy, hormone therapy, radiation, and target therapy. Often, two or more different options will be used to treat ovarian cancer.

Prevention

Routine gynecologic care with a primary care provider is an important component of cancer prevention. As part of an annual wellness exam, providers can help screen for familial cancer syndromes by reviewing the patient's family history and any new health changes. Risk reduction for ovarian cancer can also be discussed including quitting smoking and managing weight to prevent obesity. Those with a known familial cancer syndrome or those at risk should be identified during these routine exams and referred to a gynecologist oncologist and genetic counselor to discuss other options for prevention including chemoprevention, mastectomy, and bilateral salpingo-oophorectomy.

Screening

The yearly well woman exam is an excellent time to evaluate a patient's risk for hereditary breast and ovarian cancer syndromes. Using screening questions to identify those at greater risk is an opportunity to also discuss risk reduction.

The practice bulletin published by ACOG [74] outlines criteria that if met would prompt a clinician to refer a patient for a genetic risk assessment. Genetic risk assessments include a referral to a genetic counselor who will, with the patient's assistance, gather a medical family history and provide education about specific cancers including potential genetic testing and counseling. Women who have a known or suspected ovarian cancer should also be referred to a genetic counselor.

Screening methods for ovarian cancer include measurement of the tumor marker CA 125, serological markers, and ultrasound.

Consensus is that women at average risk should not undergo routine screening for ovarian cancer. The USPSTF gives an evidence level of D for screening asymptomatic women with no known hereditary cancer syndrome [75]. The incidence and prevalence of ovarian cancer makes consideration of a high false-positive rate very important when consider screening. A potential risk of screening is a false-positive result, which may lead to surgery including laparotomy or laparoscopy and other invasive procedures. Benefits include being able to find ovarian cancer at an earlier stage where it may be more curable. A large trial in the United States showed that screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian

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cancer mortality and 15% of women who had a false-positive result who underwent surgery had a serious complication [76]. The USPSTF, in their recommendation against routine screening, notes that screening may lead to patient harm, including from invasive procedures such as surgery [75].

Screening with the CA 125 tumor marker and transvaginal ultrasound in women with a familial ovarian cancer syndrome who have not had a prophylactic salpingo-oophorectomy is recommended by the National Comprehensive Cancer Network. However, improved survival rates with this screening combination have not been demonstrated [77, 78]. ACOG recommends bilateral salpingo-oophorectomy at age 35–40 for BRCA1 carriers and at 40–45 for BRCA2 carriers. However, this timing should be individualized based on patient factors, including family history, and desire for future childbearing [79]. Additional screening methodologies may be recommended, and all screening should be directed by a gynecologist or gynecologist oncologist.

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Benign Breast Conditions and Disease

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Introduction

Benign breast disease is a common occurrence in family medicine. Patients may present with masses, skin lesions, breast pain, breastfeeding complaints, and concerns regarding risk of malignancy. The incidence of benign breast disease rises in a woman's third decade of life and peaks in her fifth and sixth decade of life, whereas the risk of malignancy continues to increase past menopause [1]. Knowledge of basic anatomy and physiology of the breast is important when evaluating breast pain, nipple discharge, breast skin lesions, and breast masses. As with many other conditions, pertinent history taking and physical exam help determine the need for imaging. Many breast conditions may need confirmation with biopsy with those results dictating appropriate follow-up.

Anatomy and Physiology

The breast contains glandular, ductal, fibrous, and fatty tissue. Each breast contains 6–20 lobes made of several lobules within which are 10–100 subsegmental ducts, 20–40 segmental ducts, and 5–10 primary milk ducts that emerge at the areola via 6–10 pinhole openings. More lobes are present in the outer quadrants, especially the upper outer quadrants that are a common location for many breast conditions. Hormonal effects on breast tissue include estrogen on the development and elongation of ductal tissue, progesterone on ductal branching and lobulo-alveolar development, and prolactin on milk protein production [2]. The cyclic nature of estrogen and progesterone during the menstrual cycle increases cell proliferation and can yield changes in breast size and consistency.

History, Physical Exam, and Initial Workup

A patient may present with complaints of pain, nipple discharge, skin lesion, and/or a palpable mass. The initial assessment of breast complaints includes thorough history taking, a clinical breast exam, consideration for imaging, and possibility of biopsy.

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Table 1 Elements of history for breast complaint

Symptom characteristics
Onset of symptoms/mass
Change in symptoms/mass over time and relation to the menstrual cycle (if premenopausal)
History of similar symptoms
Discharge: Spontaneous or expressed, location, color, amount, timing with pregnancy/breastfeeding, medications, association with visual changes and/or headaches, presence of recurrent irritation
Pain: Caffeine intake, hormonal therapy, contraception use
Diet and medications: Current medications and history of hormone therapy
Personal and family cancer history: Including breast, ovarian, endometrial, color, prostate cancer, relationship to patient, age of onset
History of breast surgery or biopsies: Document reason and pathology results
Patient information: Reproductive status, reproductive history, lactation status, radiation or chemical exposure, tobacco exposure

Adapted from Andolsek and Copeland [3]

History

A patient with breast complaints should have a thorough history taken to include the duration of symptoms, presence or absence of nipple discharge, pain, skin lesion or palpable mass, change in size of any masses over time, relation of symptoms to menstrual cycle, and systemic symptoms such as fever, malaise, or chills. Potential personal risk factors for benign breast disease would generally depend on the particular lesion as discussed later in the chapter. Potential risk factors for malignant breast disease include female sex, older age, genetic factors, ethnicity, personal or family history of cancer, menstrual and reproductive history, use of hormonal medications, chest radiation exposure, diethylstilbestrol (DES) exposure, and certain benign breast disease. Elements that should be obtained from a thorough history are listed in Table 1.

Breast Self-Examination

While self-identified masses or lesions warrant a clinical exam, there is conflicting current opinion regarding regular self-breast exams. In 2009, the US Preventive Task Force (USPSTF) recommended against teaching breast self-examination (BSE) in all women (Grade D) due to false-positive findings leading to the need for unnecessary imaging and biopsies [4]. However, the USPSTF, American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the National Comprehensive Cancer Network recommend teaching breast self-awareness by educating patients about the normal feel and appearance of their breasts [4, 5].

Clinical Breast Exam

Similar controversy exists to the utility of the clinical breast exam (CBE) as a screening tool. The USPSTF has concluded that there is insufficient evidence to perform a CBE as a screening tool in women over the age of 40 in countries that provide routine mammography screening again citing the concern of high rates of false-positive results, and subsequent workup may offset potential benefits [6]. The American Academy of Family Physicians concurs that there is insufficient evidence to recommend CBE as a screening tool [7]. Additionally, the ACS no longer recommends the CBE as a screening modality [8]. However, ACOG recommends CBE every 1–3 years from ages 20 to 39 and annually after age 40 [9]. Although debate also exists for the timing and frequency for screening exams, CBE should be performed with any breast-related complaint. CBE has a sensitivity and specificity of 49–69% and 86–99%, respectively [10].

The breast exam includes visual inspection, palpation, and nipple expression. In addition to the breast, the exam should include evaluation of the chest, axillae, and regional lymph nodes. With the patient in the seated position, hand on the waist, conducts a visual inspection for breast asymmetry, size difference, contour changes (dimpling or flattening), skin color, or changes in nipple appearance. Positioning the patient with arms overhead and then on the waist while leaning forward can enhance subtle changes such as skin retractions. Skin changes suggestive of a malignancy include dimpling, puckering, edema, and thickening of the skin (peau d'orange).

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Breast palpation should be performed with the patient in both seated and supine positions. While still seated, palpate for cervical, supraclavicular, and axillary lymphadenopathy. In the supine position, the ipsilateral arm to the breast should be placed over the patient's head. The breast tissue is examined using the finger pads and progresses in a systematic fashion (either in a spiral fashion or vertical stripe pattern) without missing any areas, including up to the collarbone and axilla. Palpitation of the nipple includes attempting nipple expression by gently compressing the areola between the thumb and index finger. Consider sending any fluid expressed for evaluation. Clearly document all abnormal findings to include location (by quadrant or in relation to the face of a clock), consistency of any masses (soft, firm), mobility, and margins (well circumscribed, smooth, irregular). Benign lesions are typically without skin changes, smooth, soft to firm texture, mobile, and with well-defined margins, while malignant lesions generally are hard, fixed, immobile, and with poor margins [8, 10].

Imaging

Diagnostic imaging should be performed for any concerning masses. Imaging method is determined by patient's age due to breast density changes over time: women over 30 years of age or younger patients with a higher risk of cancer and palpable breast mass should be initially evaluated with diagnostic mammography with ultrasound [10]. Women under 30 should be evaluated with ultrasound due to increased sensitivity of detecting lesions in dense breast tissue [10]. Breast magnetic resonance imaging (MRI) is not recommended for routine breast cancer screening in women with average risk of developing breast cancer. The ACS recommends MRI screening for women at an increased risk of breast cancer defined as 20–25% or greater lifetime risk of developing breast cancer according to family history risk assessment tools, known BRCA1 or BRCA 2 gene mutations, first-degree relatives with BRCA mutations and without personal genetic testing, a history of chest radiation between the ages of 10 and 30, and genetic syndromes such as Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome or an affected first-degree relative [8]. Findings on breast imaging are summarized using the Breast Imaging-Reporting and Data System, or BI-RADS [11]. The most recent update combines all three imaging modalities (ultrasound, mammography, and MRI) to standardize reporting results and provide recommended follow-up imaging and/or biopsy guidelines summarized in Table 2.

Table 2 BI-RADS categories

BI-RADS category	Assessment	Likelihood of malignancy	Follow-up recommended
0	Incomplete	n/a	Additional imaging required, in some states within 30 days
1	Negative	n/a	Routine screening
2	Benign finding(s)	n/a	Routine screening
3	Probably benign	<2%	Short-interval follow-up (repeat mammogram in 6 months) or biopsy
4A	Low suspicion for malignancy	2–10%	Biopsy should be performed
4B	Moderate suspicion for malignancy	10–50%	Biopsy should be performed
4C	High suspicion for malignancy	>50% to <95%	Biopsy should be performed
5	Highly suggestive of malignancy	>95%	Biopsy should be performed and urgent referral to subspecialist
6	Known biopsy-proven malignancy	n/a	Surgical excision when clinically appropriate

Adapted from Salzman et al. [10]

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Tissue Sampling

Breast tissue sampling may be indicated for suspicious lesions even with normal mammography, as pathology such as lobular carcinoma may not be visible on imaging. Other indications include breast cysts that recur after aspiration, bloody nipple discharge or bloody cyst fluid, skin changes, asymmetry or thickening on exam, nodularity on exam, inflammatory skin changes that do not respond to antibiotics, suspicious nodes, or microcalcifications on mammography.

Biopsies of suspicious lesions are often performed after diagnostic imaging by a qualified physician. Options for tissue sampling include fine-needle aspiration (FNA), core-needle biopsy (CNB), or excisional biopsy. Localizing modalities include ultrasound, x-ray or stereotactic imaging, and MRI. Considering what type of sampling technique is the clinical discretion of the performing clinician and may also depend on the breast size.

Needle biopsy is performed percutaneously with local anesthesia and is a minimally invasive evaluation of abnormalities. FNA allows for diagnosis and treatment of breast cysts, cytological evaluation of abnormal lymph nodes, or when needle biopsy is not possible. CNB utilizes either a vacuum-assisted or automated biopsy devices. Both FNA and CNB allow for marking the biopsy site with a clip for future follow-up or to guide surgical excision. With adequate sampling, an FNA has 98–99% sensitivity, 99% positive predictive value, and 86–99% negative predictive value in detecting malignancy. However, adequacy is dependent on the physician's training and experience level [12]. Ultrasound-guided CNB has a sensitivity of 99% for palpable lesions and 93% for nonpalpable lesions [12]. However, excisional biopsy should be considered for evaluation and diagnosis of breast masses in addition to providing therapeutic measures. Excisional and incisional biopsies are performed when masses are suspected to be malignant, when less invasive sampling is inconclusive, unavailable, or suggestive of malignancy.

In addition to particular BI-RADS results, certain benign lesions should be considered for biopsy. A complex sclerosing lesion greater than 10 mm should be considered for excisional biopsy. Low-risk lesions including fibroadenomas (simple or complex), hamartomas, fat necrosis, sclerosing adenosis, columnar cell change or hyperplasia, or radial scar less than 10 mm do not necessarily need surgical evaluation unless there is radiographic discordance or it is associated with atypical ductal or lobular hyperplasia. All high-risk lesions that cannot be sampled should be referred for surgical excision [13].

The Triple Test

The triple test includes clinical exam, imaging, and tissue sampling. When performed with concordant results, diagnostic accuracy approaches 100% [12]. Any discordant results may require excisional biopsy. The Triple Test Score (TTS) may aid in interpretation of discordant results. Each component of the test (exam, imaging, tissue sampling) is assigned a score: 1 for benign findings, 2 for suspicious lesions, and 3 for malignant lesions. A score of 3–4 is consistent with benign lesions and may be clinically followed with a repeat exam in 4–6 weeks; >6 indicates possible malignancy that may require surgical intervention. Excisional biopsy is recommended for a TTS of 5 [12]. An approach to management of palpable breast masses is summarized in Fig. 1.

Common Chief Complaints

Breast Pain (Mastodynia/Mastalgia)

Breast pain makes up 66% of breast complaints and can be categorized as cyclical (relating to menses) or noncyclical [10] (Table 3).

Cyclic Versus Noncyclic Breast Pain

Cyclic breast pain correlates to the menstrual cycle typically occurring in the late luteal phase and resolving with menses. It occurs in two-thirds of women, and absence of serious disease can be

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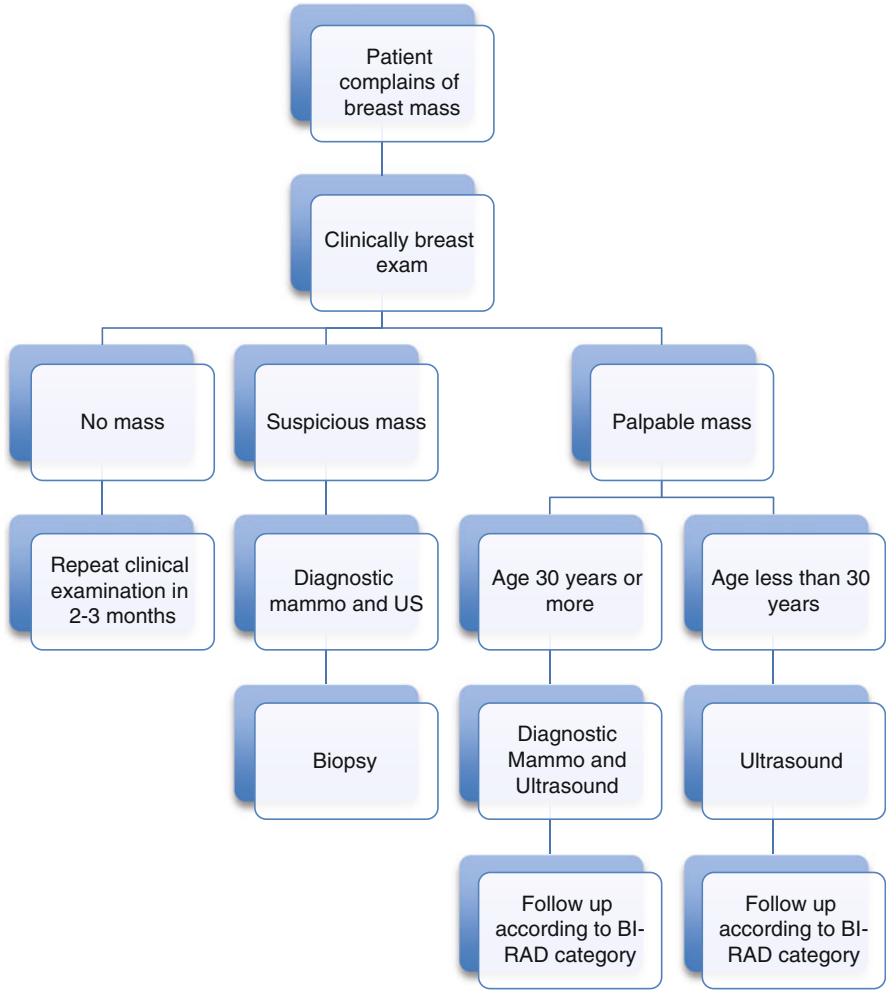


Fig. 1 Management of breast masses (Adapted from Neal et al. [13] and Pearlman and Griffin [14])

offered. Noncyclic breast pain is not correlated with the menstrual cycle and can be due to pregnancy, mastitis, thrombophlebitis, benign or malignant tumors, trauma, hematoma, and cyst rupture or fat necrosis. Though most cases of noncyclic breast pain occur for reasons unknown, they are likely due to anatomic rather than hormonal causes. Noncyclic breast pain can also be attributed to some medications such as hormonal medications, psychiatric medication, cardiac/antihypertensive medications, and antimicrobials [16].

In the initial evaluation of breast pain, it is vital to perform an examination for evaluation of palpable masses which may be contributing to symptoms. If there is a palpable mass associated with the patient's pain, referral to a breast surgeon for surgical treatment is more likely to be efficacious regardless of the pattern of pain symptoms.

Treatment of Breast Pain

Nonpharmacological Interventions

Many women wear improperly fitted bras; therefore, proper fitting of undergarments, wearing a soft supportive bra during sleep, and wearing of a sports bra during exercise may improve breast pain [16]. Cold or heat compresses and massage may also alleviate symptoms. One clinical trial

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Table 3 Summary of management of breast pain

Nonpharmacological interventions
Properly fitting bra, soft supportive bra during sleep, sports bra during exercise
Hot or cold compresses
Massage
Relaxation training
Decreasing dietary fat intake
Methylxanthine/caffeine reduction (coffee, tea, sodas, chocolate)
Vitamin E
Evening primrose oil
Pharmacologic interventions – For patients with severe persistent pain
Nonsteroidal anti-inflammatory drugs (NSAIDs) (oral or topical), acetaminophen
Oral combined contraceptives (low estrogen, high progesterone)
Danazol, low dose or during the luteal phase (FDA approved)
Gestrinone
Tamoxifen, low dose or during the luteal phase (not FDA approved)
Bromocriptine (Parlodel)
Goserelin (Zoladex) and Buserelin

Adapted from Andolsek, Copeland [3] and National Comprehensive Cancer Network [15], and AAFP [10]

demonstrated a reported decreased of symptoms in 61% of women who listened to audiocassettes of progressive muscle relaxation for 4 weeks compared to 25% in women who did not. Dietary changes decreasing dietary fat and methylxanthine/caffeine intake have been suggested; however, to benefit from a lower dietary fat diet, women must decrease their intake to less than 20% of their daily caloric intake, and there is inconsistent evidence to support the reduction or elimination of caffeine in treating breast pain.

Pharmacological Interventions

Vitamin E (alpha-tocopherol) may alter steroidal hormone production and acts as an antioxidant. However, studies have been inconclusive when used for treating fibrocystic breast disease, and it may increase bleeding risk. Evening primrose oil (gamma-linolenic acid), 3000 mg/day in divided doses for 3–6 months, is often recommended for the treatment of breast pain though conflicting data exists regarding its efficacy. Its mechanism includes restoration of the saturated/unsaturated fatty acid balance and decreased steroidal hormone sensitivity since women with cyclic breast pain may have abnormal fatty acid profiles that may cause epithelial hormonal hypersensitivity. Adverse reactions include nausea, bloating, and lowering seizure threshold; thus, it should not be used in patients with a seizure history. Isoflavones, genistein, and daidzein found in soy bind to estrogen receptors and can increase the follicular phase of the menstrual cycle to delay menstruation as well as decrease mid-cycle-luteinizing and follicle-stimulating hormone surges and estradiol levels. Evidence supporting its use is limited. Studies are limited regarding the efficacy of acetaminophen or nonsteroidal anti-inflammatory medications (NSAIDs) for breast pain though oral and topical preparations may be of benefit in those without contraindications though evidence is not consistent for benefit. The best evidence for these preparations is for the topical NSAID diclofenac (Voltaren) which has been shown to be useful in cyclic and non-cyclic breast pain [17].

Hormonally Active Pharmacological Interventions

Hormonally active medications most often used for breast pain are danazol, bromocriptine, or tamoxifen. Possible adverse reactions must be weighed against the potential benefits, and these agents are typically used for 2–6 months then tapered or discontinued. Relapse may occur requiring a second course of the same or different agent.

Danazol is a gonadotropin production and luteinizing hormone surge inhibitor and a weak estrogen antagonist. Currently, it is the only Food and Drug Administration (FDA)-approved medication for breast pain. Initial dosing is 200–600 mg by mouth daily with a maintenance dose of 50–100 mg by mouth daily once symptoms are controlled. This medication is contraindicated for pregnant, lactating patients, as well as those with

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history of VTE. Common side effects include headache, nausea, emotional lability and depression, fluid retention, vaginal dryness, hirsutism, amenorrhea, weight gain, menstrual irregularities, hot flashes, and acne. Side effects may be lessened with use of 200 mg by mouth daily only during the luteal phase. Treatment can be stopped after 4–6 months with a favorable treatment response lasting for months to years. Clinical trials have shown 59–92% of women reporting relief with danazol therapy with corresponding decreased breast volume and density.

Bromocriptine acts as a prolactin inhibitor/dopamine agonist and can be used for cyclical breast pain. Dosing is 1.25 mg by mouth nightly or 2.5 mg by mouth twice a day. Common side effects include nausea, vomiting, postural hypotension, constipation, and dizziness. Severe symptoms limit its use to women that are unresponsive to other agents or with hyperprolactinemia.

Tamoxifen is a selective estrogen receptor modulator commonly used off-label for breast pain. Dosing is 10–20 mg by mouth daily for 3–4 months or for days 15–25 of the monthly menstrual cycle. Adverse effects include menstrual irregularity, menopausal symptoms, vaginal dryness or discharge, endometrial cancer, and deep vein thrombophlebitis. In controlled trials, tamoxifen demonstrated a reduction in pain in 71–96% of women with cyclic mastalgia and 56% of women with noncyclic mastalgia. Unfortunately there is a high rate of recurrence of symptoms after discontinuation of treatment and the maximum duration of treatment is 6 months.

Gestrinone, a synthetic 19-nortestosterone derivative, has been shown in a double-blind, placebo-controlled study to yield reduction in breast pain at a dose of 2.5 mg by mouth per week. Its action is similar to danazol, and side effects are primarily androgenic.

If oral contraceptives (OCP) and menopausal hormone medications appear causative to breast pain symptoms, the addition of progestational agents (i.e., medroxyprogesterone 5–10 mg 10 days prior to menses, progesterone cream daily the week prior to menses; topical, oral, or parenteral preparations) or switching to a low-estrogen, high-progesterone OCP can relieve cyclic breast pain.

Lastly, gonadotropin-releasing hormone agonists such as goserelin and buserelin (available as subcutaneous implants) induce significant ovarian suppression, and use is limited due to significant menopausal side effect profile. There are some limited data to support the use of goserelin specifically for severe treatment-refractory mastalgia; however treatment duration is limited to 6 months due to effects on bone mineral density [18].

Nipple Pain

The complaint of nipple pain commonly occurs with the onset of breastfeeding. Breastfeeding mothers experiencing pain should have their technique evaluated. Assuring proper positioning and latch as well as releasing the infant's suction prior to removing from the breast are keys to prevention. A certified lactation consultant can be pivotal to the support of the breastfeeding couplet. Topical vitamin E ointment and USP modified lanolin are commonly used but can lead to local skin reactions. Signs of nipple cracking, fissures, blistering, or redness should be examined promptly as well as the infant's mouth. See section on "Mastitis" for further details. If a *Candida* infection is suspected, the nursing mother should receive a course of an oral antifungal, and the infant should be treated as well if topical involvement is present.

Nipple pain in the non-lactating female may be due to local irritation and friction as seen in runners. Small elastic bandages over the nipples and lubricants can be used during activities to reduce the incidence and emollients, or low-dose hydrocortisone creams may decrease symptoms.

Dermatologic conditions can also cause nipple pain. Eczema can manifest as bilateral erythema, scaling and weeping crusts, fissures, vesicles, excoriation, or erosions and can be treated with trigger avoidance and topical steroids. If nipple lesions do not resolve or are accompanied by a mass, then prompt evaluation should be performed. Further evaluation should be undertaken if the lesion is ulcerated or weeping in a middle-aged or older woman as this may suggest Paget's disease of the breast.

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Mastitis

Acute mastitis, also known as puerperal or lactation mastitis, commonly occurs within the first 3 months of breastfeeding as a result of cellulitis of the interlobular connective tissue within the mammary gland [1]. Incidence ranges from 7% to 11% of breastfeeding mothers with a higher incidence in first-time mothers. The most common organisms are staphylococcus and streptococcus species. Risk factors for mastitis include improper nursing technique leading to milk stasis, nipple fissuring/cracks allowing entry for bacteria, stress, and sleep deprivation contributing to a weakened immune system and poor milk production [1]. Presentation includes fever, flu-like symptoms, axillary adenopathy, purulent drainage, and leukocytosis. Acute mastitis can develop into abscess formation in approximately 10% of cases and rarely septicemia.

Treatment for mild infection includes warm compresses, oral acetaminophen, and oral antibiotics (i.e., dicloxacillin, a first-generation cephalosporin, or clindamycin for at least 10 days). Feeding techniques should be observed, and improper techniques corrected. Women should continue to nurse or pump frequently unless unable to achieve a good latch. Nursing can continue with intravenous antibiotics and abscess drainage if a good latch is achieved. Cultures of breast milk or purulent material are of little clinical value except when the infection does not respond to conservative management or oral antibiotics. Close follow-up in 48–72 h is warranted, and biopsy should be considered for atypical presentations or persistent/recurrent infections unresponsive to antibiotics.

Recurrent subareolar abscess (Zuska's disease) is a rare bacterial infection of the breast due to squamous metaplasia of one or more lactiferous ducts that obstructs keratin plugs and causes proximal duct dilation. It is characterized by a triad of draining subareolar cutaneous fistulas; chronic thick, pasty nipple discharge; and a history of multiple, recurrent mammary abscess. It is associated with smoking. Treatment includes abscess drainage and excision of the affected duct and sinus tract [1].

Granulomatous mastitis can be due to infection (tuberculosis), foreign material (silicone or paraffin), or systemic autoimmune disease. Microbiologic, immunologic, and histopathologic evaluation is needed for diagnosis. "Idiopathic granulomatous mastitis" describes granulomatous lesions without an identified cause. Recommended treatment includes surgical excision and steroid therapy. Since 50% of cases continue with persistence, recurrence, and complications, long-term follow-up is necessary [1].

Ectopic or Absent Breast Tissue

The most common congenital breast abnormality is supernumerary and aberrant breast tissue. The most common location is near the breast and on the chest wall, vulva, and axilla although documented occurrences have been reported outside of the milk line including the knee, thigh, buttock, face, ear, and neck. Variances in nipple components (polythelia) and glandular tissue (polymastia) occur and usually have a separate duct system from normal breast. Ectopic breast tissue responds to physiological changes similar to normal breast tissue, and malignancies in ectopic breast tissue are rare [1].

Underdeveloped breast tissue can be congenital or acquired. Congenital disorders associated with hypoplasia include ulnar-mammary syndrome, Turner's syndrome, congenital adrenal hyperplasia, and Poland's syndrome that are associated with breast cancer. Acquired hypoplasia is usually a result of trauma or radiotherapy. Amastia, the absence of breast and nipple, and amazia, the presence of nipple but absence of breast tissue, are rare [1].

Nipple Discharge

Nipple discharge occurs in nearly 7% of women referred for breast disorder evaluation with approximately 5% having serious underlying pathology [2]. Pathologic findings include discharge in postmenopausal women or women

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over 50 years old, persistent discharge, spontaneous discharge, discharge from a single-duct, unilateral discharge, gross or occult bloody discharge, clear or serous discharge, or discharge associated with a mass [10].

Galactorrhea

Galactorrhea is defined as milk production more than 1 year after breastfeeding wean or in nulligravid or postmenopausal women. It is most commonly caused by hyperprolactinemia from pituitary tumor, hypothyroidism, or medications such antipsychotics, metoclopramide, opiates, cocaine, and some antihypertensives [19]. Other causes include renal disease and chest wall inflammation from a thoracotomy, burns, herpes zoster, or topical irritation from clothing. Evaluation involves a thorough history, characteristics of the discharge, and laboratory evaluation including renal function, prolactin, and thyroid-stimulating hormone (TSH) levels. Imaging may be needed. Treatment with dopaminergic agonists can be initiated if prolactin and TSH levels are normal [2].

Non-galactorrheal Discharge

Non-galactorrheal, or non-milky, discharge warrants investigation based on the number of ducts involved. Single-duct etiologies include intraductal papilloma, ductal carcinoma in situ, and Paget's disease, thus warranting further investigation. Multiple duct discharge can be due to fibrocystic changes or ductal ectasia (discussed below) and requires further workup if bloody; otherwise, reassurance can be provided for clear, serous, green-black, or non-bloody discharge that commonly occurs with fibrocystic disease [2]. If the discharge is bloody, galactography can be performed to evaluate for space-occupying lesions. Cytological evaluation of discharge fluid has a 35–47% sensitivity for detecting malignancy and may be of limited diagnostic value.

Mammary Duct Ectasia

Mammary duct ectasia (periductal mastitis or comedomastitis) is a chronic inflammatory reaction resulting in permanent ductal distension. It presents with thick, white or discolored, cheesy nipple discharge; palpable subareolar mass; noncyclic breast pain; or nipple inversion or retraction though it can also be asymptomatic. It can be identified as microcalcifications on mammography. Mammary duct ectasia can mimic invasive carcinoma especially in middle-aged to elderly parous women and may have an association with smoking. Though biopsy may be required to exclude malignancy, mammary duct ectasia should be managed conservatively [1].

Benign Breast Masses

Risk factors for developing benign breast masses include both genetic influences and environmental exposures. On pathologic examination, benign breast lesions are frequently found to have loss of heterozygosity [2]. Population studies have shown that first-degree relatives of patients with breast cancer have a higher rate of benign breast disease [20, 21]. In addition to increased risk of breast cancer, women with BRCA1 or BRCA2 genetic mutations have a high rate of multiple benign lesions [2].

Hormonal factors likely play a large role in the development of breast lesions. Postmenopausal use of estrogen replacement (regardless of concomitant progestin use) may more than double the risk for benign breast lesions [2]. Conversely, tamoxifen use for breast cancer prevention is associated with a 28% decrease in prevalence of benign lesions [2]. OCPs have also shown a decreased risk [21]. Early studies have shown that serum levels of estrogen, insulin, C-reactive protein, and adiponectin are independent risk factors for benign proliferative breast disease although investigation is needed [22]. Some studies have shown that lifestyle modifications such as increased physical activity; increased intake of vegetable oils, nuts, vitamin E, and fiber; and decreased consumption of alcohol, animal fat,

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and red meat may lower risk of benign breast disease [23].

Benign breast masses are broadly categorized into three histological categories: nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasia. This grouping correlates to future risk of developing cancer as the degree of cellular proliferation is related to an increased risk of breast cancer in patients with benign breast conditions [24]. Nonproliferative disease carries no increased risk of breast cancer, but proliferative disease without and with atypia has a relative risk of 1.3–1.9 and 4.1–5.3, respectively [14]. Findings on biopsy, age at biopsy, and family history of breast cancer are risk factors for breast cancer for those diagnosed with benign breast masses. Additional risk factors include increased breast density on mammography, high postmenopausal plasma levels of free estradiol and testosterone, and greater than 20 kg (44 lb) weight gain after menopause, early menopause, early menarche, and late childbearing [2].

Statistically, nine out of ten new nodules in premenopausal women are benign [2]. The vast majority of biopsies (approximately 70%) will demonstrate nonproliferative lesions [1]. Current recommendations suggest that all women with a dominant, discrete, palpable lesion should have surgical referral in addition to imaging based on age and risk factors as described above. If nodularity is vague, thickened, or asymmetric, an exam can be repeated at mid-cycle for one or two menstrual cycles in the premenopausal patient. If resolved, reassurance can be provided; otherwise, the patient should be referred to a surgeon with breast imaging.

Nonproliferative Lesions

Nonproliferative lesions are further divided and include fibrocystic changes of cysts and ductal ectasia, mild hyperplasia, nonsclerosing adenosis, periductal fibrosis, simple fibroadenomas, lobular hyperplasia, juvenile hypertrophy, and stromal hyperplasia. Traumatic lesions that include hematomas, fat necrosis, and lesions caused by foreign bodies are also in the category of nonproliferative lesions. Other lesions in the category include benign tumors such as hamartomas, lipomas, phyllodes tumors, solitary papillomas, neurofibromas, giant adenomas, and adenomyoepitheliomas; infections such as granulomas and mastitis; sarcoidosis; squamous and apocrine metaplasia; and diabetic mastopathy.

Cysts

Cysts are fluid-filled, round, or ovoid structures derived from the terminal duct lobular units that occur in one-third of women between 35 and 50 years old. Late menopause, hormone-replacement therapy use, and thin stature are associated with increased prevalence of cysts [2]. Cysts represent approximately 25% of breast lesions [1, 12]. Ultrasonography has the ability to distinguish fluid-filled cysts from solid lesions. Simple cysts as diagnosed on imaging (BI-RADS 2) are almost always benign; therefore, it is not necessary to aspirate these lesions [14]. Complex, complicated, or atypical cysts are characterized by internal echoes, thin septations, thickened/irregular walls, or lack of posterior enhancement on ultrasonography and can be managed with follow-up imaging. An intracystic mass/nodule should be regarded as "suspicious for neoplasm" and consideration for core-needle or surgical biopsy [1]. Non-bloody fluid can be discarded, but if recurrent, a surgical consult should be obtained. Bloody fluid should be sent for pathology, and a surgical consult placed [2] obtained.

Fibrocystic Changes

Fibrocystic changes are the most frequent benign disorder of the breast of premenopausal women between 20 and 50 years of age, encompassing 50% of clinical and 90% of histological presentations [1]. It is commonly described as "lumpy" breasts or nondiscrete, tender, or painful breast nodules in multifocal regions or bilaterally. Symptoms usually begin just prior to menses and diminish once menses start and are rare in postmenopausal

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women. Both solid lesions including adenosis, epithelial hyperplasia with or without atypia, apocrine metaplasia, radial scar, and papilloma as well as irregular cysts without discrete mass occur. These changes are thought to be a result of estrogen's predominance over progesterone [1]. FNA can provide symptomatic relief and confirm the diagnosis. Aspiration of clear or milky fluid should be followed clinically for at least 3 months to assure that there is no recurrence [1]. Bloody fluid or no fluid aspirated with a palpable mass, residual mass or thickening, or mass recurrence warrants further evaluation and possible excisional biopsy. Mammography and ultrasonography should also be performed prior to further tissue sampling.

Fibroadenomas

Fibroadenoma is the most common benign breast tumor [14]. Typical presentation is a firm, mobile, discrete breast mass, most often unilaterally, though can be multiple and have a bilateral appearance. The peak incidence is 15–35 years of age and is generally discovered by the patient [1]. These lesions tend to grow during pregnancy, in the luteal phase of the menstrual cycle, as well as in the third and fourth decades of life due to an exaggerated hormonal response [2]. If a lesion is clinically and radiographically suspected to be a fibroadenoma, biopsy may be omitted and followed with serial ultrasonography, though some surgeons may recommend that all discrete masses be biopsy proven, especially among BRCA carriers [2]. If performed, biopsy-proven fibroadenomas need not be followed by serial ultrasounds [2]. Fibroadenomas and phyllodes tumors have similar physical and radiographic features, but phyllodes tumors need excision due to risk of malignancy and high rate of recurrence [14].

Fat Necrosis

Fat necrosis of the breast typically presents as a superficial small, ill-defined, painless, or painful inflammatory mass most commonly in the periareolar region [1, 24]. Causes include accidental trauma, postoperative changes, or radiation therapy. Affected areas either enlarge, remain unchanged, or resolve spontaneously. If symptoms persist longer than 1 week, biopsy should be performed to rule out malignancy as it can also be associated with carcinoma or any lesion that provokes suppurative or necrotic degradation (i.e., mammary duct ectasia, fibrocystic disease with large cysts) [1]. Areas of fat necrosis present as oil cysts, smooth or microcalcifications, asymmetries, or spiculated masses on mammography. Findings on ultrasonography and MRI are varied and depend on the extent of fibrosis, inflammatory reaction, and amount of liquefied fat. Fat necrosis may clinically and radiographically mimic malignancy but has classic histological characteristics [1]. Needle biopsy may be indicated to further investigate findings though it may be avoided if the MRI is conclusive [25].

Proliferative Lesions Without Atypia

These include usual ductal hyperplasia, complex fibroadenomas, sclerosing adenosis, papilloma or papillomatosis, radial scar, and blunt duct adenosis.

Usual Ductal Hyperplasia

Usual ductal hyperplasia is characterized by proliferation of epithelial cells within the mammary ducts without distorting the architecture of the ducts themselves. Usual ductal hyperplasia does not confer an increase in breast cancer risk, and no additional treatment is needed [1].

Intraductal Papilloma

Intraductal papillomas may present as a breast mass; however, most women will present with serous or serosanguinous nipple discharge [1]. Presentation is during ages of 30 and 50 years [14]. A single, central papilloma is benign and does not confer an increased risk for subsequent breast cancer. However, papillomatosis (at least five

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separate papillomas in one segment of breast tissue) does increase the risk of malignancy, and therefore, bilateral diagnostic imaging and surgical referral are needed [3]. Up to one-third of women with papillomatosis will have either an existing or subsequent malignancy [14].

Sclerosing Adenosis

Sclerosing adenosis is a benign proliferative disease that can mimic carcinoma on pathology and imaging [1]. It typically presents as a palpable mass or as an incidental finding on screening mammography. No treatment or follow-up is indicated for this lesion.

Radial Scar

Radial scar is often found as an incidental finding on pathology; however, it may mimic carcinoma on imaging [1]. When discovered, patients should be referred to surgery for excisional biopsy to ensure benign diagnosis due to the increased risk for malignancy [14].

Atypical Hyperplasia

Atypical hyperplasia encompasses both atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). ADH confers up to fivefold increase in risk for subsequent breast cancer [14]. Premenopausal women with ADH have a significantly higher risk of developing carcinoma compared to postmenopausal women [1]. ADH appears morphologically similar to ductal carcinoma in situ (DCIS); however, architecturally the cells only fill a small portion of the duct [1]. These lesions are often first detected by microcalcifications on mammography [1]. Due to the increased risk of subsequent cancer, women diagnosed with ADH should be closely monitored with clinical breast examination every 6–12 months, self-breast awareness, and annual mammograms [9, 26]. And for these patients are 30 years old or older, annual MRI can be considered [26]. ALH appears histologically similar to lobular carcinoma in situ (LCIS), the latter being notable for a greater degree of proliferation. ALH is most prevalent in perimenopausal women and typically found as an incidental finding on pathologic examination [1]. Unlike DCIS, ALH is not a precursor lesion to breast cancer and does not need to be excised; however, it is a risk factor for the development of future breast cancer [14].

Breast Disease During Pregnancy

The dynamic changes in estrogen and progesterone levels during pregnancy cause increased breast size, firmness, and nodularity returning to the prepregnancy state within 3 months of breastfeeding cessation. Palpable masses in a pregnant or lactating patient that persists for 2 weeks or longer should be evaluated with ultrasound. Ultrasound-guided biopsy may need to be performed for new solid mass in a pregnant or lactating patient. If biopsy is deferred, then close clinical follow-up and repeat imaging are recommended. Overall, 80% of palpable breast masses present in pregnancy are benign [27].

Fibroadenomas are the most common benign tumor in pregnancy and lactation. Due to growth that may outpace the increase in vascular supply, these tumors may infarct. Lactating adenomas, which occur in the third trimester and during lactation usually, regress after cessation of breastfeeding. Presentation is typically either solitary or multiple, mobile, and discrete lesions less than 3 cm [1]. These lesions may arise in ectopic locations such as the axillae, chest wall, or vulva and often spontaneously resolve. Surgical treatment may be needed for patient comfort, and there is no increased risk of malignancy [1].

Galactoceles are painless, palpable masses that commonly appear after the cessation of breastfeeding. They occur as a consequence of ductal obstruction and milk inspissations. Most do not require aspiration, but ultrasound-guided aspiration may be indicated if the mass is bothersome. Bloody nipple discharge can occur in the third trimester or during lactation due to minimal breast trauma along with epithelial proliferation and new

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capillary formation. Without a palpable mass, ultrasound can be performed to exclude papilloma or intraductal carcinoma. Ductography or postpartum MRI can be performed if further evaluation is needed. Mastitis has the highest incidence during the first 6 weeks postpartum [27]; see above for further details.

Male Breast Conditions

Gynecomastia

Gynecomastia is the proliferation of glandular breast tissue in men due to disruption of the estrogen to progesterone ratio [28]. It can be categorized as physiologic or nonphysiologic. On exam there is palpable, firm glandular tissue in a concentric mass around the nipple-areolar complex. Physiologic gynecomastia makes up one-fourth of cases, is self-limited, and occurs in newborns, adolescents, and older men. Nonphysiologic gynecomastia covers a wide range of diagnoses, and one-fourth of cases are due to idiopathic or unknown causes. This must be differentiated from pseudogynecomastia that is a proliferation of adipose rather than glandular tissue associated with obesity.

Nonphysiologic conditions include persistent pubertal gynecomastia, medications and substances (10–25%), cirrhosis (8%), primary and secondary hypogonadism (8% and 2%, respectively), hypothyroidism (2%), renal disease (1%), refeeding after starvation, and tumors (3%).

One-half of adolescent males experience gynecomastia typically starting between 13 and 14 years of age or Tanner stage 3 or 4 with resolution in 6 months to 2 years. Persistence beyond 2 years or after 17 years of age warrants further evaluation. If no underlying causes can be found and treatment is desired, testosterone supplementation, estrogen-receptor-modifying agents, or surgical referral are options.

A wide variety of medications are known to cause gynecomastia (see Table 4).

Antipsychotics, antiretroviral, and prostate cancer therapies are common culprits. Lavender, tea tree oil, dong quai, soy consumption of more than 300 mg per day, and *Tribulus terrestris* in performance-enhancing supplements have also been linked to gynecomastia. Regression occurs with discontinuation of causative agent within 3 months except with the use of anabolic steroids, marijuana, heroin, or amphetamines.

Table 4 Agents associated with gynecomastia

Cardiovascular medications
Amiodarone, amlodipine, angiotensin-converting enzyme inhibitors, atorvastatin, diltiazem, fenofibrate, digoxin, nifedipine, rosuvastatin, verapamil, spironolactone
Anti-infectious agents
Antiretroviral agents – didanosine, isoniazid, ketoconazole, penicillamine, metronidazole, minocycline
Hormonal agents
Estrogen agonists, estrogens – *whether taking it himself, or absorbing it from a sexual partner who uses vaginal cream or ring*, testosterone, gonadotropin-releasing hormone agonists, human chorionic gonadotropins, phytoestrogens, clomiphene, bicalutamide, nilutamide, anabolic steroids
Psychiatric medications
Diazepam, fluoxetine, haloperidol, mirtazapine, paroxetine, risperidone, tricyclic antidepressants, venlafaxine
Miscellaneous
Alcohol, amphetamines, alkylating agents, cimetidine, cisplatin, corticosteroids, etomidate, finasteride, flutamide, heroin, hydroxyzine, marijuana, meprobamate, methadone, methotrexate, methyldopa, metoclopramide, minoxidil, omeprazole, phenytoin, ranitidine, reserpine, sulindac, theophylline, vinca alkaloids

Adapted from Andolsek and Copeland [3] and Taboada et al. [25]

Treatment includes discontinuing any offending agents and treating underlying causes. Tamoxifen has been shown to have modest effect for physiologic, persistent pubertal, or idiopathic gynecomastia. Raloxifene, dihydrotestosterone, danazol, clomiphene, aromatase inhibitors, and surgery are other options.

Approximately 10% of patients with testicular tumors present with gynecomastia alone with Leydig cell tumors having the highest frequency due to estradiol secretion. Adrenal, testicular germ cell, liver, gastric, and bronchogenic tumors can manifest with gynecomastia as well. While

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obtaining an initial history, care should be taken to explore for constitutional symptoms that may indicate malignancy though male breast cancer accounts for approximately 1% of all breast cancer cases [29].

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Breast Cancer

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General Principles

Background

Breast cancer will be diagnosed in one in eight women in the Unites States, making breast cancer the most common cancer in women. The greater likelihood of preclinical detection of the disease, coupled with the emergence of effective treatment regimens, has resulted in declining mortality and a cure rate of over 90% for the majority of women with early disease [1, 2].

Over the past 10–15 years, there has been a paradigm shift in the clinical management of breast cancer, from a previous focus on tumor burden, to a current focus on biology-centered approaches. At the same time, there has been a trend to de-escalate more aggressive therapy and minimize possible negatives of overtreatment [3]. The present breast cancer treatment strategy involves two newer strategies:

1. Limiting targeted therapies to potential responders
2. Promoting more conservative approaches while retaining treatment efficacy

For the primary care provider, the profound ongoing changes, newer terminologies, and treatment complexities will continue to make breast cancer a challenging area [3]. There continues to be national debate and lack of consensus in many areas of breast cancer management, from screening, primary prevention with medications to newer clinical management applications: but the overall goal remains balancing the harms and benefits with input from the patient [4–6].

A patient-centric multispecialty and multimodal approach continues to be the ideal approach for the patient with breast cancer. The primary care provider's involvement is crucial in all aspects of breast cancer care, and it is anticipated that review of revised guidelines and recommendations will be requisite for the practitioner to be able to provide updated personalized care of the patient and to optimize long-term survivorship and cardiovascular health [7–12].

Definition and Classification

Majority of breast cancers (90–95%) arise from the terminal duct lobular units of the collection ducts in the breast. Epithelial cells from the ducts or the lobules begin neoplastic proliferation to produce breast cancer that is of different histological and molecular subtypes. These subtypes determine the type and response to therapy and predict prognosis in conjunction with the anatomic location and spread of the tumor [2, 4–6].

(A) **Histopathological Subtypes**: Tumors arising from the ducts of the breast tissue are known as ductal and from the lobules, as lobular. If the tumor is confined within the duct or lobule, the lesion is referred to as preinvasive, and when it extends outside the duct or lobule, as invasive. Invasive ductal carcinoma accounts for 80–85% of invasive cancers and invasive lobular carcinoma for approximately 10–15% of cases. Invasive ductal carcinoma is now referred to as "no special type" (NST). Preinvasive lesions are known as carcinoma in situ. Ductal carcinoma in situ (DCIS) can progress to invasive cancer which is typically unilateral, while lobular carcinoma in situ can be seen to occur in both breasts. The diagnosis of DCIS has sharply increased as mammography screening rates have increased but ductal carcinoma in situ does not always progress to cancer, and has variable outcomes with 40% of lesions remaining stable, while other precursor lesions can progress to invasive disease. The more recent understanding of DCIS is that the lesions are more of a risk factor, rather than definitive precursors for breast cancer.

(B) **Molecular subtypes**: At the molecular level, breast cancer is considered a "heterogeneous" disease based on gene expression: 4–5 subtypes have been described such as the Luminal A and Luminal B, Basal-like and Human Epidermal growth factor Receptor 2 enriched and Triple negative. To direct therapy, however, subtypes based on surrogate tumor receptor markers are more

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commonly used and these are categorized by the presence or absence of molecular markers for estrogen and progesterone receptors and epidermal growth factor (*ERBB2*, formerly *HER2 or HER2/neu*). Tumors expressing estrogen and /or progesterone receptors are said to be hormone receptor (HR) positive breast cancers. Approximately 70% of patients with breast cancer have HR+ disease with estrogen receptor (ER) and/or progesterone receptor (PR) expression. HR+ is more common in older women and has a better prognosis with less invasive disease. The cells can also have additional hormone receptors detected in half of the lesions. Epidermal growth factor 2 is amplified or overexpressed in 20% of breast cancers and is associated with poorer prognosis. Systemic therapy for ERBB2-targeted therapy such as Trastuzumab and Tyrosine Kinase Inhibitors has significantly changed the prognosis lately. Triple negative tumors do have hormone receptors or overexpress ERBB2. Approximately 15% of all breast cancers are triple negative and associated with lower survival and a greater likelihood of early metastatic spread. This tumor subtype is more likely to be seen in younger women, African-American or Hispanic race.

Anatomical Subtypes: The eighth edition of the American Joint Committee on Cancer breast cancer staging manual was implemented in 2018. The traditional surgical Tumor/Node/Metastases (TNM) stage of breast cancer was preserved but added into a total of seven items for the complete stage grouping. TNM refers to the size and spread of the primary breast tumor: Stage 1 is local tumors smaller than 2 cm, Stage 2–3 are local larger tumors, and Stage 4 refers to distant metastatic spread. Prognostic biomarkers added to the stage grouping include Tumor Grade, HR status, ERBB2 and Oncotype DX Breast Recurrence Score. Staging for breast cancer is more complex than for any other cancer, with more than 150 combinations of anatomic and prognostic staging groups possible [1, 13].

Pathogenesis

Molecular pathogenesis: The exact mechanism of breast cancer pathogenesis is not known, and the current evidence indicates that there are two pathways, low-grade and high-grade. The low-grade pathway consists of the estrogen receptor phenotype, and estrogen stimulates the growth of cancer cells. The high-grade pathway consists of ERBB2 and triple negative with specific genetic changes and expression of genes involved in cell cycle and cellular proliferation. In the early phases of cancer genesis, the immune system protects against cancer spread; however, once it becomes invasive, this immune microenvironment is altered to promote cancer spread [3].

Epidemiology

Breast Cancer in Females: The majority of the breast cancer diagnosed is in women over 65 years of age, with a median age of 62, and only 5% of all breast cancers occur in women under 40 years old [1, 2]. In the United States in 2018, breast cancer accounted for 30% of cancer cases and 14% of cancer related deaths with an estimated 266,120 new cases of breast cancer, and an estimated 40,920 women deaths from breast cancer [14]. The 5-year survival rate of breast cancer is an estimated 89.7%, ranging from 98.7% when cancer is diagnosed at localized stages to 27% when distant metastases are present. The overall mortality rate from breast cancer has been steadily declining over the past 50 years, for a total decline of 40% through 2017 [1].

In the United States, despite similar incidence, higher mortality is seen in African American women compared to any other ethnic group. Incidence rates have increased among Asian/Pacific Islander, non-Hispanic African American, and Hispanic women [1, 5].

Breast Cancer in Males: Less than 1% of all breast cancers occur in men. Similar to women, male breast cancer risk increases with age. Other risk factors include radiation exposure, *BRCA1/2* gene mutations, family history of breast or ovarian cancer, Klinefelter syndrome, testicular disorders,

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diabetes, gynecomastia, and obesity [1]. The vast majority of male breast cancers on histology are ductal carcinomas. Overall mortality is higher in males due to older age and more comorbidities [1, 3].

Approach to the Patient

Early Detection

Breast cancer can be diagnosed early in the disease process and is typically found prior to the development of widespread lesions and metastatic spread. Concurrently, effective treatments are widely available in high income countries, making population screening a viable option. As a result of these two important factors, patients at increased breast cancer risk can be identified early with (1) risk factor assessment and (2) screening. This has been the standard of care for the majority of the adult female population in developed countries and correlated with decreased breast cancer mortality [2–4].

Risk Factors and Risk Assessment

The main risk factors for breast cancer are female sex and advancing age. Although other characteristics have been associated with an increased risk of breast cancer, most women in whom invasive breast cancer is diagnosed do not have many other identifiable risk factors. Genetic factors account for 5–10% of increased risk [5, 6].

(A) Genetic factors such as positive family history and deleterious gene sequence from BRCA genes and other account for 5–10% of risk of which the BRCA1 and BRCA2 are the most common. The cumulative risk with age for carriers of the BRCA1 and BRCA2 by age 80 is an average cumulative risk of breast cancer of 72% and 69%, respectively, and at age 70 years, 65% and 45%, respectively.

(B) Lifestyle and other modifiable factors are emerging factors that increase the risk of breast cancer by estimates of 20% or more, and include alcohol, obesity, physical inactivity, and poor nutrition. Physical activity and breast feeding are associated with reduction in risk [3].

Additional risk factors include African American ethnicity for increased cancer mortality, early onset of menarche, nulliparity, and late onset of menopause. Hormonal contraception may increase the risk and remains to be determined conclusively. Local factors such as previous breast biopsy, breast density, prior medical radiation to the chest and previous history of breast cancer are associated with an increased risk of developing breast cancer.

Screening Models for High Risk Assessment

Genetic Risk: The new recommendation from the USPSTF is to conduct routine risk assessment, genetic counseling, and genetic testing for BRCA related cancer screening in high-risk women with personal or family history of breast, ovarian, tubal or peritoneal cancer. One of several brief questionnaires can be used. Routine risk assessment, genetic counseling, or genetic testing is not recommended. Pretesting genetic counseling is preferable. This recommendation was based on evidence that current genetic testing can accurately detect known BRCA1/2 mutations [5, 15].

Overall Risk: In the original Gail model risk factors included age, age at first menstruation, age at first childbirth, family history of breast cancer in first-degree relatives, number of prior breast biopsies, and history of atypical hyperplasia. Newer models include race/ethnicity, prior false-positive mammography results or benign breast disease, body mass index or height, estrogen and progestin use, history of breastfeeding, menopause status or age, smoking, alcohol use, physical activity, education, breast density, and diet. Most models report performance slightly better than age alone as a risk predictor. Additional annual MRI screening may be indicated if risk is greater than 20%.

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Radiological Screening: The mammogram has been the mainstay of radiological screening and the standard of care. Breast ultrasound and MRI are additional modalities for screening in certain patients with additional risk factors. Breast self-examination and clinical breast examination are no longer recommended by the majority of guidelines. Shared decision-making regarding breast cancer screening between the provider and the patient is optimal, since many of the choices are highly personal [1–3, 5].

Mammogram Guidelines: For women 50–74 years, there is general agreement regarding the benefits of screening at intervals of 1–2 years, and various guidelines are available. There is lack of consensus regarding age of onset of screening, intervals between screening and optimal imaging for dense breast tissue, as well as stopping rules. Tailored breast cancer screening for above average risk women is yet to be clearly established (Table 1).

The American college of radiology–Breast Imaging and Reporting and Data system (BI-RADS) is a standardized reporting system on mammogram reports. BI-RADS 0 category assessment is that additional imaging evaluation is needed, BI-RADS 1 and 2 indicate negative and benign findings, BI-RADS 3 is probably benign, with follow-up recommended, BI-RADS 4 is suspicious abnormality, and BI-RADS 5 is highly suspicious and tissue sampling with a core biopsy is recommended. BI-RADS 6 is for known biopsy proven malignancy.

Ultrasound is useful for evaluation of localized symptoms and preferred initial imaging in young women. Guided percutaneous biopsy is possible. Breast ultrasonography can also be used to evaluate and biopsy axillary lymph nodes. Ultrasound is often used as the imaging modality following a screening mammogram with BIRADS 2 or BIRADS 3 result.

Magnetic Resonance Imaging provides further information in addition to mammogram of suspicious lesions and can be used for screening in women, with an estimated lifetime risk of breast cancer of greater than 20%. MRI is beneficial in the evaluation of suspicious lesions in women with breast implants and for preoperative assessment of newly diagnosed invasive lobular cancer.

Harms of Screening: The harms of screening include false-positive or overdiagnosis, anxiety, and over treatment. The balance of benefits versus harms of breast cancer screening is controversial. The risk-benefit balance appears to improve with age. A 2013 Cochrane review found that it was unclear if mammographic screening does more harm than good, in that a large proportion of

Table 1 Mammogram recommendations for women based on age

Organization	Age (years)	Recommendations for women
United States Preventative Services Task Force (USPSTF)	40–49 50–74	Individualized Every 2 years for years
American Cancer Society	40–54 >55	Annually Transition to biennial or continue annually Continue screenings with overall good health and 10-year life expectancy
Canadian Guidelines	40–49 50–69	Not recommended Every 2–3 years
European Guidelines	45–74	Every 2–3 years
American College of Obstetricians and Gynecologists (ACOG)	25–39 >40 50 >50–75 >75	May be offered Annually (initiate if patient desires) Initiate no later than Annually or biennially Based on shared decision making
International Agency For Research On Cancer	50–74	Beneficial with risk of overdiagnosis
National Comprehensive Cancer Network	25–39 >40	Every 1–3 years Recommend at age 40 annually

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women who test positive turn out not to have the disease [16]. US Preventive Services Task Force found evidence of benefit of screening for breast cancer in women 40 to 70 years of age, to reduce the mortality from advanced breast cancer disease. Much of the controversy stems from the diagnosis of DCIS and treatment of lesions that may not necessarily progress to invasive disease [1, 5, 17].

Diagnosis

Overview

Imaging studies are typically suggestive of malignancy; however, definitive confirmation can only be done with a tissue biopsy. The differential diagnosis of breast cancer consists of mainly benign diseases of the breasts such as fibrocystic disease and rarely, other malignant tumors [2, 4].

History and Clinical Presentation

More than half the breast cancers are diagnosed at an early stage with a mammogram. A palpable lump that can be felt is now seen in only one third of cases, and 90% of cases are early without spread. Majority of the occurrence of breast cancer is seen to be localized at the time of diagnosis, with regional spread to the axilla seen in 31% and distant spread in only 6%. A lump in the axilla, change in breast shape, nipple changes or discharge, and dimpling of the skin changes are uncommon presentations. Metastatic disease may include bone pain, enlarged/palpable lymph nodes, palpable abnormalities in the ribs, spine, or skull.

Diagnostic Workup

Features worrisome on a screening mammogram for malignant tumor include a mass, architectural distortion, asymmetry, and microcalcifications, which require further work-up with a diagnostic mammogram, ultrasound, core needle biopsy, and sometimes breast magnetic resonance imaging. For younger women, or in the presence of increased breast density, an ultrasound may be an additional imaging modality.

Biopsy

A definitive diagnosis requires histopathological confirmation with a biopsy of the concerning tissue. There are standard criteria to establish the diagnosis of preinvasive or invasive ductal or lobular cancer. Surgical reports provide information about the peritumoral vascular invasion and surgical margin status.

Treatment

Overview

Due to the many complexities of breast cancer therapies, a multidisciplinary and individualized plan for each patient needs to be developed with patient preferences and patient reported outcomes to guide the treatment. The modalities of treatment are surgical, radiation, or systemic [1, 2, 4].

Ductal Carcinoma In Situ

The optimal treatment for DCIS continues to be debated as there is no certain way to determine the prognosis of a DCIS lesion. Surgical excision of the lesion with either mastectomy or lumpectomy may be done, often with sentinel node biopsy, and may be combined with adjuvant radiation therapy and /or hormonal therapy. However, it is unclear whether surgery or adjuvant radiation therapy for DCIS is always required. In approximately 60% and 75% of DCIS, hormone receptor positive is detected, and endocrine therapy can be administered for 5 years. Several clinical trials are currently underway to determine optimal management and identify prognostic biomarkers [1, 2, 4].

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Operable Stage I–III Disease

Loco-Regional Treatment

The surgical resection of the primary tumor is the treatment of choice for curative breast cancer and can consist of lumpectomy or mastectomy, with breast tissue conservation preferred. Sentinel node biopsy or dissection of axillary lymph nodes is done in early breast cancer to evaluate any spread to the axillary lymph nodes or to remove regional tumor spread. The sentinel node biopsy is preferred over the axillary node dissection, since there is less likelihood of lymphedema and other complications. Breast reconstruction can be offered concomitantly with the initial surgery or as a staged procedure. Patients who undergo lumpectomy and those with high-risk disease postmastectomy usually receive adjuvant radiation therapy. This reduces the risk of local recurrence and improves disease free and overall survival for patients with early breast cancer with lymph node involvement by 75% in a dose-effect relationship. Regional nodal irradiation can improve outcomes in select patients and is used as an alternative to Axillary Lymph Node dissection. Strategies to de-escalate the burdens of radiation and newer protocols, including shorter or single intraoperative dose, continue to be developed.

Systemic Therapy

Systemic therapies – endocrine or chemotherapy – have proven to be highly effective and reduce breast cancer mortality in early breast cancer by one third. Therapy is precisely determined by biomarkers, and adverse effects are limited by restricting use to only those patients with a high likelihood of a response. Therapy may be given preoperatively (neoadjuvant), or following definite loco-regional treatment, postoperatively (adjuvant).

Endocrine therapy stops or slows the growth of breast cancer by blocking the interaction of hormones, estrogen and progesterone. Because these therapies tend to be more selective for cancer cells, they usually result in fewer adverse effects. For HR+ tumors, standard adjuvant endocrine therapy after surgery is recommended for all postmenopausal women for 5–10 years with selective estrogen-receptor-modulator such as oral tamoxifen, letrozole, anastrozole, or exemestane. When managing premenopausal patients, Tamoxifen and Zoladex have been used.

The indications for chemotherapy are determined by gene expression panels (such as Oncotype DX, PAM 50, and MammaPrint) for assessment of risk of distant recurrence. The Oncotype Dx 21-Gene Recurrence Score is used most widely in the United States, for patients with early-stage HR+ or ERBB2 + breast cancer. Regimens for chemotherapy include Adriamycin, cyclophosphamide, and Docetaxel, for 12–20 weeks. For triple negative tumors and ERBB2 + breast cancers, neoadjuvant chemotherapy is the standard of care and side effects include cardiac toxicity. Bone modifying agents such as Bisphosphonates and RANK-L antibody Denosumab may serve a dual purpose of improving bone mineral density and improved patient outcomes.

Inoperable Stage IV Metastatic Disease

With rare exception, metastatic breast cancer cannot be cured, and the intent is preserving quality of life with systemic therapies, local palliative resection or radiation therapy for bone, brain, or soft tissue metastases. Trastuzumab has dramatically improved patient outcomes in ERBB2 + metastatic breast cancer. Immunotherapy and “checkpoint” medications are poised to change the dire prognosis.

Surveillance and Follow-up Care

The majority of patients with breast cancer are enjoying long periods of disease-free years, returning to their primary care providers for their long-term care. Surveillance is needed quarterly for the first year, and annual for the next 5 years, with a screening mammography, or breast MRI for high-risk patients. The early onset of menopause may occur with antiestrogen use in younger women. Posttreatment local side effects include

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lymphedema, reactions at the site of radiation or surgery, acute toxicities such as hair loss, nausea and fatigue, and chronic persistent conditions, such as infertility, premature menopause, cardiotoxicity, neuropathy, cognitive dysfunction, and chronic pain. Between 25% and 60% of women develop chronic pain. Serotonin and norepinephrine reuptake inhibitors may be useful for vasomotor symptoms, chronic pain and fatigue. Financial and psychosocial burdens are additional aspects that may need to be addressed. There is a small but increased risk of other cancers in these patients. Impaired cognition after chemotherapy is common and treatment includes cognitive rehabilitation therapy. Patients with treatment-induced menopause are at risk for bone loss and should be monitored. Primary care clinicians should counsel patients about the importance of maintaining a healthy lifestyle, monitor for posttreatment symptoms that can adversely affect quality of life, and monitor for adherence to endocrine therapy [11].

Evolving Role of Primary Care in Breast Cancer

Chemoprevention

The USPSTF now recommends that clinicians offer to prescribe breast cancer risk-reducing medications, such as Tamoxifen, Raloxifene, or Aromatase Inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects (recommendation grade B), but not for average risk for breast cancer (recommendation grade D) [6].

Breast Cancer and Cardiovascular Disease

While mortality rate from breast cancer is 1 in 31.5 women, the mortality rate for women with heart disease is 1 in 3.3 women. For older women, cardiovascular disease (CVD) poses a greater mortality threat than breast cancer itself. This is the first scientific statement from the American Heart Association on CVD and breast cancer. The optimal management of cardiac disease in survivors of breast cancer, hence becomes the foremost priority for primary care providers [17].

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Selected Disorders of the Female Reproductive System

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Ashley Wilk, Ashley Falk, and Niyomi DeSilva

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Acute Pelvic Pain in Women

Background

Pelvic pain is a common presentation in primary care. Although studies are lacking, estimates are that 1 in 7 women has acute or chronic pelvic pain in their lifetime. Causes of acute pelvic pain include reproductive, genitourinary, gastrointestinal, and musculoskeletal etiologies [1]. Various definitions for acute pelvic pain exist, but most agree chronic pelvic pain is present for at least 6 months [2]. This section will focus on acute pelvic pain and an evidence-based approach using clinical history and physical examination skills.

History

An accurate and thorough history is key to the evaluation of acute pelvic pain. First, it is important to classify patients by those of reproductive age versus those who are postmenopausal. The patient should be asked about the quality, intensity, location, timing, duration, and radiation of the pain as well as the exacerbating and alleviating factors. Inquiry should also be made into associated symptoms (urinary, gastrointestinal, and musculoskeletal). Past medical and surgical histories should be obtained, with special attention to gynecologic or abdominal pathology. Sexual history should be taken with emphasis on last menstrual period, sexual partners, and history of sexually transmitted infections [3].

Physical Exam

The physical exam should first assess the immediacy of the patient's condition. Attention to vital signs and abdominal exam may reveal fever, hypotension, tachycardia, guarding, or rebound on abdominal exam. These findings prompt immediate surgical referral as they could indicate ruptured ectopic pregnancy, hemorrhagic ovarian cyst, or ruptured appendicitis.

The clinician must then determine if the woman's symptoms are from an abdominal or pelvic source, which can be done through physical exam. It is critical to first assess for evidence of peritoneal irritation. Signs of peritoneal irritation include involuntary guarding, rebound tenderness, and increased pain with an increase in intra-abdominal pressure, such as with movement or cough [4]. Following the abdominal exam, a pelvic exam should be performed for further assessment of the patient's symptoms. The examination should begin by visual inspection of the external genitalia. Speculum examination is necessary to visualize the cervix and vagina. Abnormal vaginal or cervical discharge should be noted and sample obtained for further evaluation. Gonorrhea and chlamydia testing should be performed at this time. Bimanual exam should be performed next. One should take note of the position of the uterus and any masses or tenderness. Cervical motion tenderness commonly represents peritonitis of the reproductive tract but may also reflect irritation of adjacent structures. There are definite limitations to pelvic examination including experience of the examiner, patient anxiety, and body habitus [5].

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Labs

All premenopausal patients should receive a urine pregnancy test as part of the evaluation. Urine b-hCG tests are sensitive to 25 mIU per mL and positive 3–4 days after implantation [6]. A vaginal wet mount should be obtained and ideally interpreted with microscopy to assess for presence of *T. vaginalis*. White blood cells on wet mount would support a diagnosis of pelvic inflammatory disease (PID). Gonorrhea and chlamydia testing should be performed. Studies have found that vulvovaginal samples are more sensitive than endocervical samples for detecting chlamydia in both symptomatic and asymptomatic women [7]. Vulvovaginal samples were also found to have the highest sensitivity for detecting gonorrheal infection in a similar study [8]. Other laboratory studies are ordered based on physical exam and history findings. Leukocytosis may be seen in PID, appendicitis, and pyelonephritis, and thus if suspected, a CBC should be obtained. Studies have found that only 60% of women with PID have leukocytosis [9]. Blood type and cross-matching should be performed if there has been substantial hemorrhage. In the pregnant patient, Rh testing is performed if there is concern for threatened abortion [4]. Blood cultures are performed if there is concern for disseminated infection. Urinalysis and culture are performed when a patient has urinary-related complaints.

Imaging

Imaging modalities such as ultrasonography, computerized tomography (CT), and magnetic resonance imaging (MRI) are excellent choices in the evaluation of acute pelvic pain due to their high accuracies [10]. The American College of Radiology (ACR) recommends transvaginal and transabdominal ultrasound in the evaluation of acute pelvic pain in both pregnant and nonpregnant patients in the reproductive age group. An MRI is second line in this population if ultrasound is inconclusive or nondiagnostic. CT abdomen and pelvis with contrast should be used only in nonpregnant, reproductive age patients if MRI is not available, as radiation dosage should be taken into consideration. CT, however, demonstrates the improved diagnostic performance in identifying gastrointestinal and urinary etiology of pelvic pain. CT scan is 95–100% sensitive in diagnosing appendicitis, whereas transabdominal ultrasound is approximately 67% sensitive. IV contrast is required for optimum accuracy in diagnosing pyelonephritis, pelvic venous thrombosis, and most bowel pathologies [11].

Diagnosis/Management

To determine the etiology in a woman presenting with acute pelvic pain, the clinician must utilize the diagnostic tools discussed above. Top priority is to rule out life-threatening conditions, such as ectopic pregnancy, ruptured tubo-ovarian abscess, and appendicitis [3].

The Pregnant Patient

Ectopic pregnancy should be considered in all pregnant women presenting with abdominal or pelvic pain. Women with history of previous ectopic, tubal surgery, and tubal pathology or who have an intrauterine contraceptive device in place are at an increased risk of ectopic pregnancy. Transvaginal ultrasound is the imaging modality of choice. Early referral is recommended given surgery is the principal treatment option [12].

The most common cause of abdominal or pelvic pain in the pregnant patient is spontaneous abortion. These women often present with dull or cramping pain that may be either constant or intermittent. Vaginal bleeding may be an accompanying symptom. The cervical os should be visualized on speculum exam, which can then be used for classification of the abortion. Pelvic ultrasound is instrumental in the diagnosis. These findings will guide the management either medically or surgically [13].

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Infectious Gynecologic Causes of Pelvic Pain

Endometritis

Endometritis, an infection of the lining of the uterus, may occur postpartum or as part of an ascending infection. Women with recent instrumentation of the endometrial cavity such as hysteroscopy or dilation and curettage are at increased risk of endometritis as are women with a previous episode of PID preceded by confirmed infection with chlamydia or gonorrhea. Symptoms of endometritis typically include pelvic pain, general malaise, abnormal vaginal discharge, and bleeding. Postpartum endometritis is associated with fundal tenderness and foul-smelling vaginal discharge. Fever may be present. Antibiotics, both parenteral and oral, are the mainstay of treatment. Due to the polymicrobial nature of endometritis, a combination of broad-spectrum antibiotics with both gram- positive and gram-negative coverage is recommended. Providers should also consider adding metronidazole, given as a reported association between bacterial vaginosis and endometritis [14].

Pelvic Inflammatory Disease (PID) and Tubo-Ovarian Abscess (TOA)

PID is most common in women aged 20–29. Clinically, the diagnosis has been made based on abdominal tenderness with or without adnexal or cervical motion tenderness on bimanual examination, with supporting laboratory findings. Studies have found that clinical symptoms are not as sensitive or specific as laparoscopy [15]. The CDC recommends empiric treatment for PID in sexually active women if they are experiencing pelvic or lower abdominal pain if no cause is identified for illness other than PID in a patient with cervical motion tenderness, uterine tenderness, or adnexal tenderness. To further enhance the specificity of the minimum criteria and support a diagnosis of PID, the patient should also have either an elevated temperature (>101 F), abnormal cervical or vaginal discharge, increased numbers of WBCs on wet prep, elevated ESR, elevated CRP, or documentation of infection with *N. gonorrheae* or *C. trachomatis*. The recommended outpatient treatment is 250 mg of IM ceftriaxone in a single dose plus 100 mg of doxycycline twice daily for 14 days with or without 500 mg metronidazole twice daily for 14 days. An alternative to doxycycline is 1 gm of azithromycin once a week for 2 weeks [14].

Tubo-ovarian abscess is a complication of untreated PID; however, women over age 40 and those with IUDs in place are also at risk. If abscess rupture is suspected, prompt surgical evaluation is necessary. Clinical signs include hypotension, tachycardia, tachypnea, peritoneal signs, or acidosis. In the absence of evidence of rupture, surgical exploration and treatment are generally advised in women with signs of sepsis. Premenopausal women without signs of hemodynamic instability and an abscess less than 9 cm in diameter are candidates for antibiotic therapy alone [16]. Antibiotic therapy should include coverage for sexually transmitted pathogens (*N. gonorrheae* and *C. trachomatis*) as well as anaerobes. The CDC recommends a minimum of 2 weeks of antibiotic treatment and close follow-up if outpatient treatment is being considered [14].

Infectious Gynecologic Causes of Acute Pelvic Pain

See Table 1.

Noninfectious Gynecologic Causes of Acute Pelvic

Dysmenorrhea

Dysmenorrhea is a common cause of pelvic pain and is defined as painful cramps that occur with menstruation. Onset is typically 6–10 months after onset of menses. Primary dysmenorrhea refers to menstrual pain in the absence of pelvic pathology. Pelvic examination is necessary only in those individuals that are sexually active. The treatment options for primary dysmenorrhea

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Table 1 Infectious causes of acute pelvic pain

Diagnosis	Risk factors	Clinical signs	Treatment
Pelvic inflammatory disease	Sexually active IUD *N. gonorrhea/C. trachomatis* infection	Fever >101 F Abdominal pain Vaginal discharge +/− CMT on bimanual exam	One time dose of 250 mg IM Ceftriaxone +100 mg of doxycycline BID for 14 days +/− metronidazole Alternate to doxycycline is 1 gm of azithromycin q week for 2 weeks
Tubo- ovarian abscess	Typically a complication of PID, thus presentation per above.	Signs of rupture Hypotension Tachycardia Tachypnea Peritoneal signs Acidosis	If hemodynamically unstable, surgical consultation is advised If abscess less than 9 cm give 250 mg ceftriaxone x 1 dose, 100 mg doxycycline BID for 14 days and metronidazole 500 mg BID for 14 days
Endometritis	Postpartum Postoperative (D&C, hysteroscopy) Previous gonorrhea/ Chlamydia infection	Fundal tenderness Foul-smelling vaginal Discharge +/− fever	Hospital admission with broad spectrum antibiotic (gram positive and gram negative) +/− metronidazole

include nonsteroidal anti-inflammatory drugs and hormonal contraceptives. Secondary dysmenorrhea should be suspected when additional symptoms such as abnormal uterine bleeding, dyspareunia, and noncyclic pain are present and when pelvic examination is abnormal, thereby suggesting an underlying pathology. Further evaluation of secondary dysmenorrhea should start with transvaginal ultrasound once infectious etiologies, such as gonorrhea and chlamydia, have been ruled out.

Endometriosis is the most common cause of secondary dysmenorrhea. Pelvic exam may reveal retroversion, decreased uterine mobility, adnexal masses, or uterosacral nodularity. The pain of endometriosis is typically cyclical and may be associated with dyspareunia, dysuria, and dyschezia. Adenomyosis is associated with menorrhagia with possible intermenstrual bleeding. Bimanual exam is likely to reveal an enlarged, tender, boggy uterus in adenomyosis. Leiomyomata presents with cyclic pelvic pain with menorrhagia, and fibroids may be appreciated on pelvic examination. The treatment of dysmenorrhea associated with endometriosis is combined oral estrogen-progesterone; however, depot medroxyprogesterone, the etonogesterel implant (Nexplanon), and the levonorgestrel-releasing intrauterine device (Mirena) have also been proven effective [17].

Ovarian Cysts

Functional ovarian cysts are relatively common in women of reproductive age; they tend to be asymptomatic and resolve over the course of 4–8 weeks with expectant management. The rupture of a follicular cyst causes a release of fluid, which may cause acute pain due to irritation of the peritoneum. The pain may be severe initially; however, it resolves without treatment. Corpus luteum cysts, being more vascular, can lead to severe hemorrhage and pain similar to a ruptured ectopic. Stable patients were previously evaluated through surgical laparoscopy if the diagnosis was not certain; however, CT scan can replace the diagnostic laparoscopy. Hemodynamic compromise, uncertainty of torsion, symptoms unrelenting for over 48 h, increasing hemoperitoneum on ultrasound, or decreasing hemoglobin are indications for surgical intervention [18].

Adnexal Torsion

Adnexal torsion is an uncommon gynecologic emergency that occurs when the ovary, fallopian tube, or both twist on the utero-ovarian ligament. Prompt diagnosis is necessary to ensure surgical restoration of the blood supply in order to salvage the ovary and tube. This is often difficult as it presents similarly to other pelvic and abdominal conditions and the imaging

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features associated with torsion may be nonspecific. The patient typically presents with acute onset abdominal pain. Other clinical features are leukocytosis, nausea/vomiting, palpable abdominal mass, and fever. Doppler studies should be performed in addition to ultrasonography if torsion is suspected, as lack of arterial or venous flow to/from the involved adnexa is often seen. A normal Doppler study does not necessarily rule out adnexal torsion. Ultrasonography with Doppler has been shown to be more accurate in diagnosing adnexal torsion compared with CT scan in some studies [19].

Nongynecologic Causes of Acute Abdominal Pain

Gastrointestinal

Appendicitis is the most common nongynecologic cause of acute pelvic pain. Patients generally present with right lower quadrant abdominal pain with migration of pain from the periumbilical area. Fever, psoas sign, rebound tenderness, and rigidity may also be found on physical examination. If the diagnosis remains unclear, imaging studies with either ultrasonography or CT are useful in making the diagnosis.

Diverticulitis should be suspected in the adult patient with left lower quadrant abdominal pain, fever, and leukocytosis. Patients with suspected diverticulitis are often evaluated with CT scan, which is useful if the differential also includes appendicitis [1].

Urinary Tract Disorders

Pyelonephritis, lower urinary tract infection, and nephrolithiasis can lead to acute pelvic pain. Lower urinary tract infections usually present with dysuria, urgency, frequency, and suprapubic tenderness. Urinalysis and culture can confirm the diagnosis, and the patient can be treated with appropriate oral antibiotics. Similar symptoms are often seen in pyelonephritis with the addition of fevers, chills, and costovertebral angle and flank tenderness. If uncomplicated, outpatient management with appropriate antibiotics is warranted.

Nephrolithiasis often presents with severe, colicky pain which radiates from the flank into the pelvis. Associated nausea and emesis may be seen. Urinalysis is positive for blood, and imaging studies reveal the stone and a dilated ureter or kidney. Expectant management with pain control and IV or oral hydration is the mainstay of treatment [15].

Conclusion

In the evaluation of acute pelvic pain, the clinician must first rule out the emergent, life-threatening conditions. Given the broad differential, a complete and thorough history, physical examination, and urine pregnancy test are indicated in every patient presenting with pelvic pain. Ordering the appropriate labs and imaging as discussed above will often lead to the correct diagnosis and treatment.

Toxic Shock Syndrome

Menstrual toxic shock syndrome (TSS) emerged as a public health threat to women of reproductive age in 1979–1980. While sporadic cases have been documented since the 1920s, the dramatic increase in the number of cases in the 1980s prompted research that determined an association with high-adsorbency tampons. The incidence of TSS has declined after some of the brands of tampons were discontinued [20]. TSS is caused by a specific strain of *S. aureus* that produces toxin TSST-1 and enterotoxins A–E. The toxins act as superantigens stimulating a release of cytokines, prostaglandins, and leukotrienes. CDC reports TSS to include symptoms of fever (temperature greater than 102), diffuse macular erythroderma, desquamation (1–2 weeks after the onset of rash), hypotension, and involvement of three or more organ systems [21]. Nonmenstrual TSS is most often a result of postsurgical, postpartum, postabortion, or nonsurgical cutaneous infections (Table 2).

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Table 2 Diagnosis of toxic shock is based on the presence of two major criteria, or one major criteria and one minor criteria

TSS major criteria (all must be present)	Minor criteria (three or more)
Fever (temp >102 F) Rash Erythroderma followed by desquamation of mucous membranes: oral, vaginal and conjunctival Hypotension (systolic BP < 90)	CNS: Altered mental status w/o focal deficit Cardiovascular: Distributive shock, arrhythmia, nonspecific ST wave EKG changes, and heart failure Pulmonary: Pulmonary edema, respiratory distress syndrome Gastrointestinal: Nausea, vomiting, and diarrhea hepatic Elevated liver-associated enzymes renal: Elevated blood urea nitrogen Hematologic: Thrombocytopenia, anemia, leukopenia musculoskeletal: Creatinine kinase greater than twice the upper limit of normal Metabolic: Hypocalcemia, hypophosphatemia

Chronic Pelvic Pain

Background

Chronic pelvic pain (CPP) is defined as a nonmenstrual, noncyclical pelvic pain that has been present for at least 6 months. Further, it is defined as not being related to malignancy. CPP must be severe enough to interfere with daily activities and may often require medical or surgical treatment [22–29]. Reported prevalence rates range from 3.8% to 24% in women aged 15–73 years [29], roughly 15% of the female population [30]. Pelvic pain is the single most common indication for referral to gynecology [31]. The economic impact, including both direct and indirect health care costs, exceeds 2 billion dollars a year in the USA [29, 31]. CPP is often associated with negative behavioral, cognitive, sexual, and emotional consequences [32], as well as increased drug and alcohol use [24, 29]. Patients with CPP are more likely to have a history of spontaneous abortion, military service, c-section delivery, sexually transmitted disease, nongynecologic surgery, nonpelvic somatic complaints, multiple sexual partners, and psychosexual trauma and abuse [23, 25–27, 30, 33].

The pathophysiology of CPP is poorly understood and is often multifactorial. CPP is rarely found to be due to a single cause [31]. An underlying diagnosis is not found in up to 60% of patients with CPP [29, 30]. Symptoms are often suggestive of urinary tract, gastrointestinal, pelvic floor, or gynecological sources [34]. This complex interaction of organ systems, along with the psychological burden associated with chronic pain, has led to the recommendation to treat pelvic pain with a multidisciplinary approach [23, 25–27, 33].

History

A thorough history is critical in evaluating a patient with CPP. A full review of systems is indicated [30], as is a full history of previous workup for the pain, including all surgical and nonsurgical diagnostic approaches [23, 30]. It is important also to discuss with the patient how CPP affects her daily activities and sexual function and satisfaction. Treatments tried in the past, both those that provided relief and those that did not, are helpful in teasing out the next steps in both diagnosis and management [23].

One should have a discussion with the patient regarding her pain, in terms of character, quality, intensity, radiation, and causative and alleviating factors [30]. It is important for the provider to differentiate between visceral, somatic, and neuropathic pain when taking a history. Visceral pain is typically reported as dull, crampy, and poorly localized. It can be associated with nausea, vomiting, and sweating due to autonomic feedback [30]. Somatic pain, because it originates from muscles, bones, and joints, will be reported as sharp or dull and is localized. Neuropathic pain is reported as burning or paresthesia [30].

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Physical Exam

The physical exam for a patient with chronic pelvic pain is similar to that for a patient presenting acutely and should be performed gently [23], and chaperones should always be present, with at least one person of the medical team being female [30]. The exam should begin with a gait analysis, paying attention to her movement and her sitting pose. Heart and lung exam, as well as appropriate HEENT exam, should also be part of this comprehensive evaluation. The abdomen should be inspected for scars, masses, and tenderness, as well as rebound or fluid shifting.

A pelvic exam should be performed last and should be performed after the patient voids [29]. Inspection of the tissues of the external genitalia is key to note discoloration, scarring, or signs of dermatologic or infectious processes [30]. A moist cotton swab can be used to determine any point tenderness of the external structures [23]. A gentle digital exam can help determine if there is pelvic floor weakness, spasms, or tenderness. A speculum exam is necessary to inspect the internal vaginal vault, and samples can be obtained for Pap smear (as appropriate), wet prep, and cultures for sexually transmitted infection testing. It is important to note the appearance of the cervix and if there is discharge present. Use of one half of the speculum with pressure placed posteriorly or anteriorly in the vaginal vault can help assess for pelvic organ prolapse. The pelvic exam is completed with a bimanual exam, noting any cervical motion tenderness and tenderness with palpation of the posterior portion of the bladder or of the ovaries and uterus themselves.

A rectal examination is also warranted in the evaluation of CPP. It should include anoscopy to evaluate for lesions, internal hemorrhoids, inflammation, fissures, fistulas, or abscesses. Colonoscopy may be warranted if the patient has a report of hematochezia or is greater than age 50. Psychological assessment should be included as part of the complete evaluation of a patient with CPP and should be performed by a health psychologist or psychiatrist who is familiar with CPP [26, 27]. Factors to be considered with this assessment include the patient's understanding and meaning of her pain; impact on her functional roles; emotional functioning; coping mechanisms; knowledge of what can exacerbate her pain; quality of her relationships with her family, friends, and care team; and social support [26, 27].

Labs and Imaging

Due to the multifactorial etiology and pathophysiology of the source of pelvic pain, a six-point system has been developed to assist the physician in guiding the workup. Named "UPOINT," it consists of recommendations for *u*rinary, *p*sychological, *o*rgan specific, *i*nfectious, *n*eurological, and *t*ender musculature causes [34]:

- *Urological*: assess urine flow and voiding diary; consider cystoscopy, ultrasound, and flowmetry
- *Psychological*: assess for depression, history of abuse, pregnancy losses, coping mechanisms (catastrophizing), and feelings of hopelessness or helplessness
- *Organ Specific*: assess genital and urinary structures and anorectal exam and asks questions regarding sexual dysfunction and stooling patterns
- *Infectious*: take samples for urine and genital infections, consider stool cultures
- *Neurological*: assess complaints of paresthesias and dysesthesias, perform neurologic testing as part of examination to include sensory reflexes, and muscular function testing
- *Tender Musculature*: assess by palpating pelvic floor muscles, abdominal muscles, and gluteal muscles

Labs that are indicated in the evaluation of CPP include b-hCG; Pap smear (as indicated by age and history of past pathology on Pap smears); gonorrhea and chlamydia testing; wet prep evaluation for yeast, bacterial vaginosis, and trichomoniasis; hemoccult testing; urinalysis; and urine culture. Other testing to consider includes ESR and CRP to evaluate for chronic inflammatory

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processes, such as inflammatory bowel disease or antitissue transglutaminase antibody tests for celiac disease [23].

Imaging commonly performed includes a pelvic ultrasound to evaluate the bladder, uterus, and ovarian structures. Transvaginal ultrasound is more sensitive to evaluate for pelvic masses and adenomyosis than transabdominal scanning [26, 27]. In other cases, an MRI may be indicated, as this was found in one study to determine the cause of CPP in up to 39% of cases [30]. MRI is useful for characterizing pelvic masses and is the imaging modality of choice for diagnosing adenomyosis [26, 27]. Laparoscopy, cystoscopy, and hysteroscopy allow direct visualization of the involved structures and can also be useful for the evaluation of CPP.

Diagnosis and Management

The four most common causes of CPP include endometriosis, adhesions (intra-abdominal/intrapelvic), interstitial cystitis, and irritable bowel syndrome [30]. Several organs and organ systems have been implicated in the cause of CPP:

- Bladder pain syndrome
- Urethral pain
- Vulvar pain syndrome
  - Generalized
  - Local
- Vestibular pain
- Clitoral pain
- Dysmenorrhea
- Pelvic floor muscle pain
- Coccyx pain
- Irritable bowel syndrome
- Chronic anal pain
- Pelvic bone stress fracture

The most common cause of chronic pelvic pain is endometriosis [30], defined as the presence of endometrial tissue outside of the endometrial cavity. Incidence is 1–7% and affects primarily nulliparous women in their 20s and 30s. Unfortunately, diagnostic laparoscopy to determine the presence of endometriosis is negative in half of the cases. Adenomyosis is defined histologically as the presence of endometrial glands and stroma deep within the stroma of the uterus. It is a condition in which the uterus is often enlarged and boggy and is associated with pain, dysmenorrhea, and menorrhagia. Adenomyosis is diagnosed with use of US or MRI and has an incidence in up to 70% of cases of CPP, occurring in the fourth and fifth decades of life [26, 27]. Adhesions can arise from chronic pelvic inflammatory disease, prior surgery, endometriosis, or unknown factors [26, 27]. Somewhat controversial as a cause of CPP, adhesions are found in up to 50% of patients undergoing laparoscopic evaluation for CPP. Up to 33% of women who suffer from CPP have a history of pelvic inflammatory disease, thought to be related to adhesions that resulted from the infection [26, 27]. Uterine fibroids are associated with pain, dysmenorrhea, pressure, and menorrhagia.

Interstitial cystitis is a nongynecological source of CPP that is manifested by bladder pain, urinary frequency, urgency, or nocturia. Pain is often suprapubic. Bladder pain syndrome is thought to be caused by a defect in the permeability of the urothelial glycosaminoglycan layer leading to mast cell activation, histamine release, neurogenic inflammation, and upregulation of afferent nerve signals. Childbirth, surgery, bacterial infections, instrumentation, or autoimmune processes are considered possible insults contributing to bladder pain syndrome. After initial evaluation to rule out infection, voiding diaries can help with diagnosis and to monitor treatment. Cystoscopy to perform intravesical potassium sensitivity has a specificity of 83% and sensitivity of 73% [23].

Irritable bowel syndrome is the presence of abdominal pain three or more days a month and is associated with changes in stool frequency or form (loose vs. solid). IBS is a diagnosis of exclusion, and other causes such as Crohn's, celiac disease, lactose intolerance, and milk/food allergies must be ruled out. Up to 79% of patients with CPP have IBS, and 60% will have associated dysmenorrhea [30].

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Treatment

Medications implicated in the treatment of CPP are primarily analgesics, such as NSAIDs. Naproxen is the preferred NSAID due to long half-life. Medications such as gabapentin and carbamazepine, phenytoin, and clonazepam have also been found to be useful as they inhibit the excessive stimulation of accessory neurons. Tricyclic antidepressants such as amitriptyline have been found to assist with CPP as well, restoring sleep and improving pain tolerance. The use of opioids in the treatment of CPP is controversial, although it may allow return of normal function of the patient if pain is controlled. Due to risk of addiction and the comorbid psychological diagnoses often associated with CPP, it is recommended that opioid use for treatment of CPP be a last resort [23] and in a tertiary center equipped and experienced for management of chronic pain [33]. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have level III evidence in the treatment of refractory pain [23].

CPP associated with endometriosis is often managed with hormonal treatment, such as estrogen-progestin combinations, progestins alone, danazol, or GnRH agonist, with or without NSAID therapy. The theory is CPP that varies with menstrual cycling will respond to the suppression of the hypothalamic-pituitary-gonadal axis.

NSAIDs are considered first line therapy for interstitial cystitis, although studies have not found NSAIDs or opioids to be routinely effective. Pentosan polysulfate sodium (PPS) is approved by the FDA for the treatment of interstitial cystitis and is thought to mimic the normal glycosaminoglycan layer that protects the urothelium that is dysfunctional. Treatment may require up to 6 months to be effective but is effective in up to 32% of patients. Dietary modifications have also been suggested in the treatment of interstitial cystitis, such as elimination of foods suspected to aggravate the urothelium including caffeine, alcohol, spicy and acidic foods, artificial sweeteners, and carbonated beverages [23].

IBS can be treated with dietary modifications. Diarrhea-predominant IBS may respond to loperamide, cholestyramine, and rifampin. Constipation-predominant IBS is treated with supplemental fiber, stool softeners, and cathartics such as lactulose and polyethylene glycol. TCAs, muscle relaxants, and SSRIs have also been helpful in treating IBS [30].

It should not be overlooked that women who suffer from CPP also may suffer from concomitant psychosocial problems as related to past history of abuse, both sexual and emotional, as well as anxiety and depression. Treatment of these comorbid conditions is key in treating the whole patient and necessary for success.

Surgical Interventions and Approach to Management of CPP

Denervating procedures, such as presacral neurectomy and uterosacral ligament resection, have been studied as treatment modalities for CPP. The results in the randomized controlled trial (RCT) are inconsistent and cannot be recommended [33].

Hysterectomy may be indicated in the treatment of CPP, and up to 18% of hysterectomies are performed for CPP [33]. Hysterectomy is an acceptable treatment for endometriosis, adenomyosis, and uterine fibroids.

Adhesion lysis was not found to be beneficial except in the setting of severe adhesions. Hydrodistention of the bladder by urogynecologists with intravesical instillations with dimethyl sulfoxide or bacille Calmette-Guérin has been shown to decrease pain.

Conclusion

Chronic pelvic pain is a multifactorial process, can involve more than one organ system, and should be treated with a multidisciplinary approach to include physical therapy for pelvic floor muscle dysfunction and psychiatry or behavioral health specialists. Successful

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treatment requires a positive patient-provider relationship. First-line medications indicated for the treatment of CPP include NSAIDs and hormone therapy for appropriate indications (i.e., endometriosis). Narcotics are not indicated in the treatment of chronic pelvic pain, except in the most extreme of cases and with the assistance of a pain management treatment facility.

Infertility

Introduction and Background

Primary care offices are often where patients with concern for infertility initially seek care. Infertility is defined as failure to achieve pregnancy within 12 months of unprotected sexual intercourse or therapeutic donor insemination in women younger than 35 years old [35]. In women over age 35, it is defined by failure to achieve pregnancy within 6 months. Several studies indicate that approximately 80–90% of couples without significant comorbidities conceive within 1 year of attempting conception, 95% after 2 years [35]. Fecundability is a term used to describe the probability of achieving pregnancy in one menstrual cycle. Fecundability has been shown to decrease after 3 months of attempted conception and decreases with the advancing age of the female partner.

Infertility affects up to 15% of opposite-sex couples in the USA [36]. Appropriate workup should be offered to patients who meet the definition of infertility or are otherwise at high risk of infertility based on additional medial conditions. Women over the age of 35 should undergo prompt workup and intervention after 6 months of failure to conceive. Women over the age of 40 and those with medical conditions known to cause infertility warrant immediate evaluation and treatment. Relevant medical conditions include amenorrhea; oligomenorrhea; uterine, tubal, or peritoneal disease; endometriosis stage III or IV; and either known or suspected male infertility [36].

Female Factor Infertility

According to the World Health Organization (WHO), female factor infertility is the etiology in 37% of cases in developed countries. Initial workup of female infertility includes review of patient's past medical and surgical history, thorough physical exam, and laboratory workup. Historical elements that should be reviewed include menstrual history (age of menarche, cycle lengths and characteristics, and signs of ovulation), previous methods of contraception, timing of sexual intercourse in relation to ovulatory cycle, sexual dysfunction, prior pregnancy history, previous surgical procedures and hospitalization, and gynecologic history (including sexually transmitted infections, pelvic inflammatory disease, abnormal Pap smears and associated treatments, endometriosis, or uterine fibroids), as well as any previous infertility workup or treatment that has been performed [36]. Endocrine history including thyroid disease, hirsutism, and galactorrhea should be addressed as well as family history of birth defects or premature menopause. Current medications and dietary supplements should be reviewed. Social history should be taken with attention to use of nicotine-containing products, alcohol, and/or illicit drugs. Physical exam should include full assessment with special attention to patient's vitals, thyroid, breasts, and pelvis. Note should be made of thyroid enlargement or nodules, signs of excessive androgens, breast secretions, and Tanner stage of sexual development. Pelvic examination should assess for vaginal or cervical abnormalities, secretions, or discharge, excessive tenderness of the pelvis, presence of masses, uterine shape, position, and mobility.

Female infertility workup evaluates structural abnormalities, ovulatory function, and ovarian reserve. Ovarian reserve is the term used to describe reproductive potential of the ovaries based on the number of oocytes available for potential fertilization [37]. Ovarian reserve can be evaluated through serum tests of a woman's level of anti-mullerian hormone (AMH) or basal follicle-stimulating hormone (FSH) plus estradiol. Transvaginal ultrasound with antral follicle count can also assist in this evaluation. Ovarian preserve

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correlates with expected response of future ovarian stimulation treatments. Ovarian reserve is considered to be diminished when AMH is less than 1 ng/mL, antral follicle count is less than 5–7, FSH is over 10 IU/L, or if there is history of fewer than 4 oocytes at the time of egg retrieval following in vitro fertilization stimulation [37]. AMH is produced by antral follicles and remains stable throughout the menstrual cycle. This allows AMH to be assessed at any point during the menstrual cycle. Diminished AMH correlates with diminished ovarian reserve. Antral follicle count can be assessed using transvaginal ultrasound to evaluate the number of follicles in both ovaries measuring 2-10 mm in size. Fewer than 5–7 follicles is considered to be a low antral follicle count. A low count is associated with a diminished response to ovarian stimulation. Antral follicle count can be low in hypothalamic amenorrhea or with hormonal contraceptives. It is elevated in the setting of polycystic ovarian syndrome (PCOS). FSH and estradiol levels should be measured between cycle days 2–5. FSH values over 10 IU/L are associated with less response to ovarian stimulation treatment. Estradiol levels assist in analyzing FSH results. Elevated estradiol levels over 60–80 pg/mL may suppress FSH levels and indicate decreased ovarian reserve [37]. Women with elevated FSH level prior to age 40 or with unexplained ovarian insufficiency should be screened to determine if they are fragile X carriers.

Ovulatory function is typically assessed with a woman's menstrual history and/or serum progesterone measurement [38]. Progesterone values greater than 3 ng/mL in the mid-luteal cycle suggest ovulation but do fluctuate over the course of a few hours. Furthermore, ovulatory dysfunction is defined as repeated levels of luteal progesterone less than 3 ng/mL, history of oligiomenorrhea/amenorrhea, or both. Up to 33% of women with regular menstrual cycles every 25–35 days are anovulatory, so ovulation must be confirmed with further evaluation. This can be performed in a variety of ways including progesterone measurement in mid-luteal cycle, positive luteinizing hormone (LH) testing, cervical mucus changes, or basal body temperatures. Possible etiology of anovulation include obesity, hypothalamic dysfunction, pituitary dysfunction, or, most commonly, PCOS. Hyperprolactinemia and thyroid disease may also cause ovulatory dysfunction including inadequate luteal phase or amenorrhea. As such, serum thyrotropin and prolactin levels should be checked during workup [38].

Gynecologic imaging can assist in evaluating fallopian tube patency, pelvic pathology, and ovarian reserve. Tubal factors are evaluated with hysterosalpingography (HSG) and hysterosalpingo-contrast sonography while uterine factors are evaluated with HSG, transvaginal ultrasound, sonohysterography, and hysteroscopy. HSG is a procedure performed to view the uterus and fallopian tubes, evaluating tubal patency. Radiopaque contrast is injected through the cervix while fluoroscopy imaging is performed. The negative predictive value of HSG to evaluate tubal patency is much higher than the positive predictive value [35].

Male Factor Infertility

Male factor infertility, according to the WHO, was reported to be the causal factor in about 10% of cases of infertility in developed countries. Overall, male factor may be contributory in up to 40% of cases in addition to the female factor. As such, evaluation for male infertility including medical history, physical exam, and lab workup including semen analysis is recommended when initiating infertility workups. Those with male infertility often are found to have no sperm or low sperm count in ejaculate, termed azoospermia and oligozoospermia, respectively. Poor sperm motility, otherwise known as asthenozoospermia, is found in nearly 80% of infertile men. Teratozoospermia, or abnormal sperm morphology, is another factor that may contribute to male infertility [39].

Etiology of male infertility can be divided into four main categories. Endocrine and systemic medical disorders account for 2–5% of male infertility cases, mostly frequently related to secondary hypogonadotropic hypogonadism. Primary testicular defects in sperm production are identified in

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65–80% of male infertility cases while sperm transport disorders account for 5%. 10–20% are without specific identifiable cause and normal sperm analysis and are termed idiopathic male infertility [39].

Workup of male fertility should focus on evaluating for potentially reversible or treatable causes. Subsequently, workup should aim to identify those who may benefit from assistive reproductive technology. Evaluation should include thorough history, physical examination, and semen analysis. It may also include endocrine testing, genetic testing, and imaging of glands and ducts [39].

Semen sample should be collected following 2–7 days of abstinence from ejaculation to allow for accurate sperm count. Since sperm concentration in semen samples can be variable, submission of two samples obtained at least 1 week apart is recommended [39].

Unexplained Infertility

Up to 30% of couples show evidence of female ovulation as well as tubal patency and normal semen analysis; this is termed "unexplained infertility." For these couples, emphasis should be placed on optimizing the overall health of both partners and timing intercourse based on ovulation. Possible treatment avenues may include stimulated ovulation with clomiphene and/or intrauterine insemination. In vitro fertilization has not been shown to be of significant benefit in couples with unexplained infertility [40].

Endometriosis

The presence of endometrial tissue outside of the uterus is known as endometriosis. It was first described over 150 years ago, and yet no unified theory of its origin exists [41]. Endometrial tissue has been found in several locations outside the uterus, including on the ovaries, fallopian tubes, posterior cul-de-sac, inside the peritoneal cavity, and on the bowel. In rare cases, it has been found within the lungs, brain, bone, and even on the skin [41–45].

Epidemiology

Endometriosis is seen in approximately 15% of all women within the reproductive age. It is the most common cause of chronic pelvic pain and 40% of infertility [43, 44]. Approximately 50% of all women with endometriosis experience infertility [46].

Risk factors include early menarche, late menopause, low BMI, Muellerian anomalies, nulliparity, prolonged menses, shorter lactation intervals, and first-degree relatives with endometriosis.

Pathophysiology

Since no single theory has been proven, the pathogenesis of endometriosis is considered multifactorial. The most widely accepted one is retrograde menstruation, proposed by Sampson in the 1920s [43]. It proposes that endometrial tissue is retrogradely transported up through the fallopian tubes and eventually into the peritoneal cavity. From there, it has the ability to implant essentially anywhere throughout the body. This was proven evident in a study where 90% of women evaluated during their menstrual cycle were found to have menstrual blood within their peritoneal fluid [44]. Coelomic metaplasia is another concept that was brought forth in the 1960s. It was theorized that the peritoneum contains undifferentiated cells which are transformed into endometrial tissue as they are influenced by endogenous hormonal or immunological factors that promote this differentiation [44, 45]. Benign metastasis is another theory that suggestion spread of endometrial cells through lymphatic or hematological distribution. Endometrial implants found in the brain, bone, and lungs are evidence of such mechanism.

Implantation of endometrial tissue in ectopic sites is not the only factor that affects endometriosis. The foreign cells need the correct environment in order to proliferate and survive. Several processes have been suggested. Impaired cell-mediated immunity prevents the clearance of ectopic endometrial cells and fragments

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[43]. Leukocytes are unable to recognize the cells as abnormal for its location and are resistant to natural killer cells [44]. The endometrial cells are further potentiated by the immune system. The increased numbers of leukocytes in the peritoneal fluid leads to increased inflammation and capillary formation which result in increased vascularization, thereby providing increased blood flow to the implanted endometrial cells. Upregulation of TNF alpha, IL-8, and cytokines helps the neovascularization and proliferation, further stabilizing the implanted tissue. VEGF has been shown to directly correlate to the stage of disease. Elevated levels of macrophages cause further inflammation due to being bound to a portion unique to endometriosis. This limits the phagocytic ability and increases the production of IL-6, leading to increased inflammation. Increased levels of prostaglandins have also been noted in peritoneal fluid, contributing to increased pain.

Infertility in endometriosis is thought to be directly linked to increased inflammation. Impaired ovulation and inappropriate oocyte formation are thought to be a result of the inflammatory state. The luteal phase is also disrupted, most likely secondary to dysregulation of progesterone receptors. Inflammation can also negatively affect sperm motility, embryo formation, and implantation.

Treatment

Treatment options for endometriosis are fairly limited and are not always effective, especially long-term. Many have side effects, leading to limited use of the treatment and subsequently immediate return of symptoms. NSAIDs and OCPs are considered first line therapy for endometriosis [46]. Pain is best controlled with NSAIDs, although there is inconclusive evidence of efficacy. They work by inhibition of COX-1 and COX-2 activity, downregulating prostaglandin production, thereby inducing endometrial cell apoptosis [46, 47]. Side effects of NSAIDs include peptic ulcers, increased bleeding risk, and anovulation [48]. OCPs inhibit gonadal estrogen which suppresses ovarian activity. The result is a reduced production of prostaglandins, thereby decreasing inflammation. Continuous use or shorter days off OCPs produce the best results as it limits the recovery phase of estrogen synthesis. Drawbacks of OCP use include increased risk of thromboembolic events in tobacco smokers over the age of 35. OCP use is limited in women who desire fertility in the near future. Unfortunately, cessation of OCPs results in an almost immediate return of symptoms.

Various other hormonal treatments have also been investigated. Progestins block mechanisms at the central and peripheral levels, leading to a decrease in estrogen-induced proliferation. The atrophic endometrium thereby enters a pseudopregnancy state, decreasing pain. Nexplanon, which is depomedroxyprogesterone, produces similar results. Side effects include possible weight gain, breast tenderness, and menstrual irregularities. Hormonal IUDs such as levonorgestrel-releasing can improve dysmenorrhea, pelvic pain, dyspareunia, and the size of the ectopic endometrial tissue. Synthetic androgen derivatives were first explored several decades ago, as they induce a hypoestrogenic-hyperandrogenic state. While they limit endometrial tissue growth, the side effects of elevated levels of androgen make this a less desirable option [46, 49].

Second-line treatment options include GnRH analogues which suppress the receptors of the pituitary. This leads to hypoestrogenism which manifests as amenorrhea and atrophy of the endometrial tissue. While up to 50% of patients experience symptom reduction, the use of GnRH analogues is limited as it can mimic menopause with hot flashes, depression, urogenital atrophy decreased libido, loss of bone density, and worsening of lipid profiles. Aromatase inhibitors decrease the levels of estrogen by downregulating the conversion of steroidal precursors. With the decrease in estrogen, endometrial tissue growth is inhibited and COX-2 mediated inflammation is reduced. Reversible side effects include headaches, nausea, diarrhea, flushing, joint pain, and stiffness, along with bone density loss. Adding HRT or bisphosphonates can help reduce the severity of the side effects. Melatonin can also

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be used as a natural antioxidant and to combat free radicals that are related to endometriosis. It has been shown to decrease the size of endometrial tissue and increase antioxidant activity. VEGF has been directly correlated to the severity of the disease. By inhibiting VEGF, angiogenesis is halted, depriving the endometrial implants of blood supply that is necessary for implantation and proliferation. Although animal studies have been conducted, no human trials have been established at this time [46, 49].

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Part XXII

The Musculoskeletal System and Connective Tissue

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Disorders of the Neck and Back

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James Winger

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Disorders of the Back

Low Back Pain (LBP)

General Principles

Definition/Background

Low back pain (LBP) is a heterogeneous condition with high prevalence, high morbidity, and large economic burden. According to the 2010 Global Burden of Disease Study, low back pain ranked highest among 291 studied disorders in terms of years lived with disability (YLDs), with a global point prevalence estimated to be 9.4% (95% CI 9.0–9.8) [1]. In 2005, direct expenditures for spine problems in the United States were estimated at $85.9 billion, which represented 9% of the total national healthcare expenditures, similar to costs associated with arthritis, cancer, and diabetes, and only exceeded significantly by those for heart disease and stroke [2]. In the United States between 2004 and 2008, it is estimated that over two million episodes of back pain resulting in presentation for emergency care occurred, yielding an incidence rate of 1.39/1,000 person-years [3]. In workers 40–65 years of age, back pain costs employers an estimated $7.4 billion/year in lost productive time [4]. Commonly, disorders of the neck and back are self-limiting conditions, which require only judicial use of imaging and rarely more invasive treatments. Many national and international groups have produced high-quality, evidence-based recommendations to aid in the diagnosis and treatment of low back pain (Table 1) [5].

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Table 1 2007 recommendations on the diagnosis and treatment of low back pain from the American College of Physicians and the American Pain Society

1. Patients should be classified at initial presentation into the following groups: Nonspecific low back pain, back pain potentially associated with radiculopathy or spinal stenosis, or back pain potentially associated with another specific spinal cause. The history should include assessment of psychosocial risk factors that predict the risk for chronic disabling back pain
2. Clinicians should not routinely order imaging or other diagnostic testing in patients with nonspecific back pain
3. Diagnostic imaging and testing should be pursued when severe or progressive neurological deficits are present or when severe underlying conditions are suspected
4. Patients suspected to have either radiculopathy or spinal stenosis should be evaluated with MRI or CT only if potential candidates for surgery or epidural steroid injection
5. Clinicians should provide patients' educational materials regarding the course and prognosis of back pain, advice to remain active, and self-care options
6. For most patients, the first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs
7. Clinicians should consider the addition of nonpharmacologic therapy with proven benefits in those not initially improving. For acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, yoga, acupuncture, massage therapy, spinal manipulation, cognitive-behavioral therapy, or progressive relaxation

Epidemiology

A 2002 survey in the United States indicated that low back pain, defined as posterior trunk pain between the costal margins and inferior gluteal folds, was present for at least 1 day in the last 3 months in 26.4% of respondents, with men and women exhibiting similar responses. Prevalence rates were reported highest among Native Americans and lowest among Asian Americans. Increasing income and higher education levels had moderating effects on reported back pain [6]. Throughout the adult life cycle, prevalence rates increase until the 60–65 year age group and then again decline, with the peak incidence of LBP in the third decade of life [7]. Commonly reported factors associated with LBP include anxiety, depression, job dissatisfaction, low levels of social support, low educational status, poor coping skills, ongoing litigation, smoking, and obesity [8]. While the incidence of LBP is increasing, as are its associated medical costs, no commensurate improvements are seen in health status [2].

Progression to chronic LBP that lasts more than 6 weeks is a costly complication, both in terms of medical expenditures and work absences. In those experiencing activity-limiting pain, most will experience recurrent episodes [7], and up to 40% of those with initial back pain episodes will experience pain chronically [9]. Psychosocial factors (depression, anxiety, coping mechanisms, attitudes, stress, and job satisfaction) better predict the transition from acute to chronic back pain than do patient-specific anatomic factors [8].

The majority of the societal morbidity associated with LBP is accounted for by disability. Disability 1 year after initial lumbosacral injury has been shown to be predicted by injury severity, specialty of the first healthcare provider seen after injury, worker-reported physical disability, number of pain sites, "very hectic" job, no offer of accommodation, and previous injury involving a month or more off of work. These factors produce a model predicting disability with a 0.88 (95% CI 0.86–0.90) area under the receiver operating characteristic (ROC) curve [10].

Natural History

LBP is frequently described as a self-limiting condition in that initial episodes resolve in 90% of individuals within 3 months of onset [9]. Pooled data analysis indicates that the greatest improvement occurs in the first 6 weeks following initial injury with slower improvement through 52 weeks. However, LBP has a high propensity for recurrence and persistence, and levels of pain, disability, and work absence remain mostly constant after 90 days. A 2008 study indicated that in a cohort of nearly 1,000 patients, more than half of those initially absent from work had returned by 14 days and 83% by 3 months; nearly 30% had persistent pain at 12 months' time [9]. Many patients experience at least one recurrence in the

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first 12 months following a low back pain episode with a prior episode of LBP being the only strong predictor of future recurrence [11].

Anatomic sites of acute lumbosacral pain vary and may include paraspinal musculature, collagenous structures (tendon and ligament), intervertebral disk, annulus fibrosus, facet joints, central canal stenosis, spinal nerve roots, and the vasculature.

Clinical Presentation

The experience of many individuals with LBP is that of pain and dysfunction that gradually resolve over several days and allow return to the usual activities of daily living [9]. Most individuals with an episode of LBP will not present to medical attention.

History

Focused history in a patient presenting with LBP will include onset of symptoms, location of pain, timing of pain, interventions that provide palliation or provocation, and any associated symptoms. Assessment for signs suggesting neurological involvement, such as radiation of pain, weakness, numbness, sensory changes, or bowel and bladder dysfunction, is likewise important. Description of any previous episodes of back pain should be elicited during the interview, as well as any current or pertinent past medical history. Interview of a patient presenting with low back pain should pay particular attention to established risk factors for back pain such as known trauma, previous low back pain, missed work, occupational mechanism, and preexisting mood disorder [12].

In addition to standard interviewing approaches, certain additional queries in individuals with low back pain are aimed at identifying neurosurgical emergency, vertebral fracture, or malignancy. A retrospective study of 206 patients with spinal cord or cauda equina compression noted that the presence of bowel and bladder dysfunction as well as saddle sensory disturbance yielded a specificity of 0.92 and a likelihood ratio of 3.46 of such compression [13]. Interestingly, this same study noted that these symptoms showed stronger association with MRI diagnosis than did physical examination of the lower extremities, even while only marginally raising the clinical suspicion of neurological compression. A 2013 study evaluating the benefit of screening questions addressing the presence of malignancy indicated that only a prior history of malignancy is informative [14]. The same study also found that prolonged corticosteroid use, older age, and trauma increased the pretest probability of spinal fracture by 15–43% when present individually and greater when present in combination. Thus, there is relatively little evidence favoring reliance on the so-called "red flag" symptoms to trigger changes in management.

Physical Exam

Examination of the patient with back pain is attentive to the presence and extent of signs indicating neurological involvement. Observation of the patient's gait, stance, and posture (absence or alteration of normal lordosis or kyphosis) may provide diagnostic clues. Inspection while attending to patient modesty should include the entire back and posterior pelvis but also the upper and lower extremities. The sequelae of trauma may present as disfigurement, edema, or ecchymosis. Asymmetry and muscle wasting may indicate chronic motor neuropathy. Palpation of bony and other landmarks may assist in the localization of a primary pain source. The spinal range of motion in coronal, sagittal, and axial planes may be useful as an indicator of which movement types trigger a patient's pain; however, this specific assessment is noted to be highly examiner dependent.

A neurologic exam is performed on all patients and should include both upper and lower extremities (Table 2). Manual muscle testing should focus on nerve root myotome testing rather than on specific individual muscles, and strength should be scored with the standard 0–5 scale. Testing of nerve root strength may be assessed as follows: single-leg rising from a chair without the use of hands (quadriceps/L4), heel walking (tibialis anterior/L5), and toe walking (gastrocnemius/S1). The examiner must be aware that deficits in balance or preexisting weakness may affect motor strength testing results. Assessment of pinprick and light touch sensation should be

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Table 2 Strength, sensation, and deep tendon reflexes associated with the commonly impinged nerve roots

Nerve root	Strength testing	Sensory innervation	Deep tendon reflexes
C5	Shoulder abduction	Lateral arm	Biceps (C5, C6)
C6	Elbow flexion, wrist extension	Lateral forearm	Brachioradialis
C7	Elbow extension, wrist flexion	Middle of the hand dorsum	Triceps
C8	Finger flexion	Medial forearm	–
T1	Finger abduction	Medial arm	–
L3	Hip flexion	Distal upper leg	–
L4	Knee extension	Anterior knee	Knee jerk (patellar)
L5	Ankle dorsiflexion (heel walking)	Dorsum of the foot	Hamstring reflex (L5, S1)
S1	Ankle plantar flexion (toe walking)	Lateral foot	Ankle jerk (Achilles)

compared to the unaffected contralateral side. Numbness should be specified by dermatomal distribution and may include examination of the perineum and sacral distributions. Evaluation of vibration and position sense may be useful if central processes are included in the differential diagnosis. Signs of upper motor neuron (UMN) dysfunction, such as Hoffmann's reflex, a positive Babinski's sign, or hyperreflexia, may suggest etiology for lower motor neuron dysfunction. Pertinent reflexes include the knee jerk (L4), hamstring reflex (L5, S1), and ankle jerk (S1), as graded on the standard 0–4 scale. Depending on the extent of neurological manifestations, assessment of perineal sensation and anal sphincter tone may be appropriate.

Nerve tension tests such as the straight-leg raise (SLR) and seated slump test (SST) may suggest neural impingement but are positive in most symptomatic individuals with and thus have a poor positive predictive value when applied to all patients with low back pain. In the SST, the patient is seated on the edge of the examination table. With the hands clasped behind the back and neck flexed with the upper body "slumped" forward, the examiner passively extends the knee. A positive finding is reproduction and radiation of the patient's pain beyond the knee. Having the patient extend his or her neck, thus relieving neural tension and lessening or relieving the pain, may provide confirmation of this finding. The SLR is performed with the patient supine and the ipsilateral hip flexed to 90° while the examiner passively extends the ipsilateral knee. A positive test is reproduction and radiation of the patient's pain prior to 60° of knee extension and further relief of such pain with knee flexion. This maneuver may be modified by Lasègue's sign: dorsiflexion of the ipsilateral ankle increasing neural tension and thus worsening the pain response. The femoral stretch test (FST) for upper (L2, L3, L4) lumbar nerve root impingement is performed with the patient prone as the examiner passively and slowly flexes the ipsilateral knee. Reproduction of the patient's typical lower extremity pain constitutes a positive test. The crossed SLR (cSLR) and crossed FST (cFST) are performed on the lower extremity contralateral to a patient's typical radiating pain.

The cSLR and cFST are poorly sensitive but highly (>90%) specific [15]. Thus, neural tension tests may be better applied only to those with presenting symptoms already suggestive of radiculopathy.

In 2011, Suri et al. evaluated the accuracy of physical exam maneuvers for the diagnosis of midlumbar (L2, L3, L4) and low lumbar (L5, S1) nerve root impingement. The study compared standardized, expert-level examinations to MRI findings in patients presenting to a physiatry spine practice with acute or subacute symptoms suggestive of nerve root impingement. Exam maneuvers testing positive that either increased the likelihood ratio >4.0 or exhibited 100% specificity for midlumbar nerve root impingement were FST, cFST, sit-to-stand test, medial ankle sensation, and patellar reflex assessment. Achilles reflex testing was the only exam maneuver in which a positive test either increased the likelihood ratio >5.0 (+LR 7.1) [15].

Further examination should include the hips and sacroiliac joints. Range of motion of the

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femoroacetabular joints should be assessed along with the response to the loading of the acetabular labra. The acronymically named FABER test, also known as Patrick's test, stresses the SI joint by flexing, abducting, and externally rotating the contralateral hip while applying posterior pressure to the ipsilateral anterior pelvis and contralateral knee. A positive response is reproduced pain in the contralateral SI joint.

Given the contribution of psychosocial issues to acute and chronic low back pain, assessment of biopsychosocial stressors should be performed. Minimally, screening for common mood disorders such as anxiety and depression should be done. The presence of nonorganic signs or nonanatomic pain distributions does not exclude orthopedic pain generators but may indicate a need for further psychiatric workup.

It is estimated that a brief physical examination and neurological examination of the L4, L5, and S1 dermatomes, myotomes, and deep tendon reflexes should be sufficient to identify 99% of potentially serious spinal pathology [16].

Radiographic and Laboratory Diagnosis

There has been much studied and written about the utilization of imaging strategies as applied to back pain. Published recommendations discourage imaging in the first 4 weeks after presentation [17, 18]. In a 2007 clinical guideline paper, the American College of Physicians and the American Pain Society wrote: "Clinicians should not routinely obtain imaging or other diagnostic tests in patients with nonspecific low back pain [5]." Supporting these recommendations, a 2009 random effects meta-analysis of 1,806 patients evaluated the effect of immediate lumbar imaging on clinical outcomes at 3 and 6 months' time when compared to usual care without imaging; no differences were found with regard to pain or function levels at the specified time points [18]. Risks of unnecessary imaging include radiation exposure (CT, roentgenography), identification of abnormal tissues with unknown relation to a patient's pain source, diminished self-perceived health, and unnecessary healthcare utilization [17].

Plain-film radiography is best used as an initial evaluation only when vertebral compression fracture is of utmost concern, such as those with osteoporosis or with chronic steroid use. When appropriate, plain-film radiography of the spine should include standing anteroposterior and lateral view of the lumbar spine. In adolescent athletes in whom spondylolisthesis is considered, oblique views of the lumbosacral spine should be obtained. European guidelines actively discourage the use of plain-film radiography and MRI for nonspecific back pain unless in the context of referral for a second opinion [19].

Advanced imaging may play an important role in the evaluation of a patient when severe (urinary retention, saddle anesthesia) or progressive neurologic deficits are present (Fig. 1) or when high-morbidity conditions such as metastatic cancer, vertebral infection, or the cauda equina syndrome are suspected [5]. Magnetic resonance imaging is generally preferred over CT due to the lack of ionizing radiation and better visualization of soft tissues and the spinal canal. In patients with signs and symptoms suggestive of nerve root compression or spinal stenosis, evaluation with MRI or CT should only be done in individuals who are potential candidates for surgery or image-guided epidural steroid injection [5].

Radiographic abnormalities are common in the spine and show poor correlation with patients' presenting pains [20]. A 2000 study of 408 patients demonstrated no significant associations between segmental distribution of symptoms and the presence of anatomic impairment, while only severe nerve compression and disk extrusion were shown to be strongly predictive (OR 2.72 and 3.34) of pain present below the knee [21].

Differential Diagnosis

Nonspecific Low Back Pain

It is theorized that the majority of acute low back pain has paraspinal anatomic structures as a pain generator. Paraspinal musculature, spinal ligaments, and annulus fibrosis of the intervertebral disk are all poorly imaged and may be sites of

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Fig. 1 Imaging of the pathologic spine. (**a**) T2-weighted sagittal MRI image of the lumbar spine of a 64-year-old man reveals multilevel spondylosis with disk pathology including protrusion and extrusion with migration at levels L3–L4, L4–L5, and L5–S1. (**b**) Plain-film x-ray image of lateral cervical spine in an 84-year-old woman shows extensive and widespread spondylosis and osteoarthritis with anterior bridging osteophytes and ossification of the anterior longitudinal ligament and moderate to severe disk degeneration. (**c**) T2-weighted axial MRI image of the lumbar spine of a 22-year-old man at the L5–S1 level demonstrates right foraminal disk protrusion and disk bulge, causing mild central canal stenosis, severe right-sided neuroforaminal narrowing, and moderate left-sided neuroforaminal narrowing with mild bilateral facet hypertrophy

injury that account for the most common types of low back pain [17].

Osteoarthritis

Degenerative osteoarthritis of the axial spine is estimated to be present in 40–85% of individuals [21], and arthritis in general is a leading cause of disability and decreased quality of life. Spondylosis (lumbar spine degeneration) has been defined as intervertebral disk degeneration and same vertebral-level osteophytosis. As in other joints, spinal arthritis is characterized by changes to the articular cartilage and subchondral bone, inflammatory response of the synovium, and inappropriate bone and cartilage overgrowth. Radiographic features of spondylosis include vertebral osteophytosis, disk space narrowing, and facet joint osteoarthritis. Recent longitudinal studies with a large number of patients have highlighted the discordance between radiographic findings and patient symptoms [21].

Intervertebral Disk Herniation

Progressive failure of the successive layers of the annulus fibrosus is responsible for the ultimate failure of the structure of the intervertebral disk. Gradual desiccation of nuclear material results in a centrifugal disorganization of collagenous layers in the inner and outer annuli. This disorganized tissue cracks and fissures, eventually

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resulting in channels that permit herniation of the nuclear material through the annulus.

Disk herniation occurs typically in a posterior (paramedian) or posterolateral direction, these being the weakest areas of the disk. Depending on the anatomic location of the disk disfigurement, resultant symptoms may border on radiculopathy (posterolateral) to frank myelopathy or neurogenic claudication (paramedian). Disk disfigurement may range from disk bulge to herniation, protrusion, and extrusion [22].

The hallmark of disk herniation presentation is radiating pain. While the outer layer of the annulus fibrosus is poorly innervated, like other chronically degenerative collagenous tissues, the pathologic outer annuli exhibit neoinnervation that show positive staining for substance P, which has been associated with pain generation [22]. Paresthesias and numbness may be present and with prolonged symptoms weakness may occur in the distal musculature from lower motor neuron compromise.

Diagnosis is commonly clinical, based on a combination of reported radicular pain in a dermatomal distribution, neuropathic signs, and positive nerve-tension testing findings. As up to 30% of asymptomatic individuals have radiographic evidence of lumbar disk pathology, radiographic study is not commonly indicated without severe or rapidly progressive neuropathic symptoms [23].

Spinal Stenosis

Degenerative lumbar spinal stenosis describes the effects of degenerative changes in the spinal canal on the vascular and neural elements of the lumbar spine [24]. Symptoms vary and may include gluteal or lower extremity pain that may occur with or without back pain, especially when seen in older patients. Walking and upright exercise typically worsen symptoms, and patients may relieve symptoms with forward flexion or recumbent posture. As in other syndromes mediated by degeneration, symptoms are slowly progressive. While not supported by extant literature, certain exam findings may be associated with the diagnosis of spinal stenosis: the Romberg test, thigh pain exacerbated by extension, sensorimotor deficits, leg cramps, and abnormal Achilles tendon reflexes all may be present. Prognosis may only be favorable in up to one half of patients, with few treatments significantly altering the course of the disease. If needed for diagnostic or interventional purposes, MRI or CT myelogram are the preferred imaging modalities.

Osteoporosis

Osteoporosis is estimated to affect up to 30% of all women over the age of 65. Associated fractures occur in up to 50% of all affected individuals, leading to profound morbidity and healthcare resource utilization. The United States Preventive Services Task Force currently recommends screening via dual-energy x-ray absorptiometry (DEXA) in women with increased fracture risk aged 60–64 and all women aged greater than 65 [25]. In addition to age and sex, risk factors include low BMI, personal history of fracture, Caucasian or Asian race, > two alcoholic drinks daily, caffeine and tobacco use, history of falls, low level of physical activity, low calcium and vitamin D intake, and use of certain predisposing medications. Initial treatment includes fall prevention education, intake of calcium >1,200 mg/day, intake of vitamin D >800 IU/day, and treatment with bisphosphonate osteoclast inhibitor medication. Compression fractures of the vertebra are the most common type of osteoporotic fracture and may be painful; symptoms usually resolve over the course of 3–4 months. Up to 4% of patients presenting to primary care offices with back pain will have a vertebral compression fracture [14]. Patients with vertebral compression fractures usually do not present with pain radiation, as there typically is no neural compromise. Plain-film radiography may indicate a loss of vertebral height associated with compression fracture, and diagnosis of low-impact fractures in susceptible individuals should prompt further investigation. Currently, there are no serum biochemical markers used to aid in diagnosis [25].

Neoplasia

Fewer than 1% of individuals presenting to primary care offices with back pain will be diagnosed with a malignancy [14], and the spine is a more common site of metastasis than primary tumor.

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Risk factors for spinal malignancy include age >50 years, history of malignancy, and recent unintended weight loss. Symptoms include unrelenting pain that is not improved with rest and may be worse at night. Initial evaluation may include plain-film radiography enhanced by the erythrocyte sedimentation rate.

Symptomatic secondary metastases are estimated to occur in approximately 10% of all cancer patients, and cadaveric studies find 30–90% prevalence of spinal metastases [26]. Spinal metastases are most likely to originate from the breast, lung, prostate, or hematopoietic system and may arise via hematogenous spread, local extension via lymphatics, or perineurium or extension through the intervertebral foramina.

Primary spinal tumors are rare, affecting 2.5–8.5/100,000 patients yearly [27]. Multiple myeloma is a malignant clonal proliferation of plasma cells characterized by the presence of these cells in the bone marrow and monoclonal immunoglobulins in the serum and/or urine. Rarely, a solitary plasmacytoma may be the only manifestation of disease and may be present in the vertebral column. These tumors commonly present with spinal cord compression; thus, serum and urine protein electrophoresis should be performed in all patients with pathological vertebral fractures in which primary malignancy is not evident. Lymphomas may arise in the bones or compress the spinal cord via invasion of the epidural space.

Facet Syndrome

The lumbar zygapophyseal joint is a commonly cited source of spinal pain; dysfunction may be associated with unilateral or bilateral pain radiating to one or both buttocks, groin, and thighs but not proceeding below the knee. Pathological degeneration of the synovial joint may be noted on CT evaluation, and thus intra-articular anesthetic injection has long been a treatment for this condition. However, as with many other areas of degeneration within the axial skeleton, there is incomplete correlation between radiographic findings and patients' reports of pain [28]. Thus, today diagnostic anesthetic block of the small nerve fibers innervating the facet joints (medial branch block or MBB) is considered a gold standard for lumbar facet joint syndrome diagnosis. Due to the fleeting response to MBB seen in treated patients, a longer-lived treatment is now utilized: lumbar medial branch neurotomy (LMBN). Thermal coagulation at temperatures in excess of 80 °C denature intracellular proteins and produce results that last on average, longer than those achieved with MBB [28]. A 10-year clinical audit noted that among 174 patients treated with LMBN, 68% exhibited good or excellent results.

Ankylosing Spondylitis

Characteristic of the spondyloarthropathies is ankylosing spondylitis (AS). It is an inflammatory arthritis that commonly affects the axial spine with possible extension to peripheral joints, eyes, and bowel. AS exhibits symptoms onset in the late teens, but the delay between the symptom presentation of lumbosacral pain and stiffness and eventual diagnosis averages 8 years [29], primarily due to the difference in distinguishing the symptoms of AS from nonspecific mechanical low back pain in the young active population. While there is limited diagnostic utility in plain-film radiology, MRI has permitted the identification of the inflammatory sequelae of this disease, aided by serum markers of inflammation such as ESR and CRP.

Visceral Diseases

Uncommonly, back pain may be the only presenting concern in a patient with organ system-based disease. Typically, visceral pain referred from intra-abdominal and retroperitoneal organs differs in quality from musculoskeletal pain; however, this difference may be subtle and overlooked.

Dissecting thoracic or abdominal aortic aneurysm is described as "tearing" pain that is acute and severe. This condition is found in up to 4% of those patients over 50 with increased prevalence in smokers and those with diagnosed hypertension and hyperlipidemia. Some patients will have a pulsatile abdominal mass, and presentation may include diaphoresis and signs of impending circulatory failure such as hypotension and tachycardia [30].

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Myocardial infarction may present as mid-thoracic pain that radiates to the left arm or axilla. It is most common in those older than 45, with risk factors including family history, hyperlipidemia, hypertension, obesity, and others. Presenting symptom constellation may include diaphoresis, dyspnea, anterior chest heaviness or pain, nausea, vomiting, and a sense of impending doom.

Acute low back pain associated with abdominal pain in a woman of childbearing age may indicate ectopic pregnancy. Back pain is described as part of a classic symptom triad including amenorrhea and vaginal bleeding. Hypovolemic shock may be present in up to 20% of cases, and associated back pain may be located in the L1 and L2 dermatomes of the pelvic organs.

Acute pancreatitis commonly presents with "boring" thoracolumbar pain when the pancreatic duct is obstructed. Patients with acute pancreatitis may have a history of gallstones or binge drinking, and diagnosis is usually achieved with assessment of serum lipase and amylase as well as CT demonstration of glandular inflammation.

Vague back pain that occurs with increasing gastric acidity levels may represent a duodenal ulcer. Inflammation, injury, and ulceration of the mucosal lining of the digestive tract are associated with *H. pylori* infection, smoking, and alcohol ingestion.

Urological conditions such as nephrolithiasis and urinary tract infection commonly present with varying back pain. Ascending urinary tract infections may exhibit low lumbar pain or perinephric pain from ribs 9–11 on either side of the low thoracic spine if pyelonephritis has developed. Unilateral thoracolumbar pain radiating to the ipsilateral flank and toward the groin may indicate a ureteral stone [30].

Management

Stratified Primary Care Management

Multiple international management recommendations for low back pain recommend stratification of patients into groups based on risk for morbid pathology and risk of progression to chronic back pain. A 2011 study known as STarT Back evaluated this model on the basis of economic and patient-centered metrics when compared to usual care in English general practices [31]. This study included greater than 850 adult patients and evaluated changes in the Roland Morris Disability Questionnaire (RMDQ) at 12 months' time as well as quality-adjusted life years (QALY) and healthcare costs between stratified and non-stratified groups. Individuals were stratified into one of three groups: "low-risk" patients had one visit and were educated as to the good prognosis and that further treatment was not necessary nor beneficial; the medium-risk group was referred for further physiotherapy; and the high-risk group was referred for "psychologically informed physiotherapy" [31]. The stratified (interventional) group had significantly improved RMDQ scores at 4 and 12 months and 0.039 additional QALYs and cost savings compared to the nonstratified control group. The low-risk group intervention was found to be noninferior to usual care, indicating that the minimum intervention did not lead to worse outcomes than the current best practices. Differences were present between matched risk groups at 4 and 12 months but lost statistical superiority at the latter time point [31].

Another study of stratification in family medicine practice demonstrated similar results. In 2014, Foster published results showing modest improvements in patient overall outcomes, improved use of healthcare resources, and reduced sick certification without increased healthcare costs. Direct patient benefits of stratification intervention included improvements to physical function, fear avoidance beliefs, satisfaction, and work absenteeism. Changes to physician behaviors included decreased NSAID prescription, increased appropriate referral to physical therapy, and fewer sickness certifications [32].

A subsequent 2018 study of 1,700 patients was unable to reproduce these positive findings and demonstrated no improvement in patient function or healthcare utilization with stratified care [33].

Thus, stratified care for low back pain may demonstrate clinical and economic benefits and can be implemented successfully into a family medicine practice. Further research may reveal if

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certain populations show improved outcomes from stratified care.

Activity

For most patients, especially those with nonspecific low back pain, rapid return to normal activities, including work, are recommended. However, these patients should initially avoid heavy lifting, twisting, and bodily vibration [5].

Bed Rest

The harmful physiological adaptations to organismal inaction are dramatic and well established. The complications of bed rest are myriad. Muscle mass loss may approach 2% daily in the first 3 weeks of enforced rest; this is primarily due to catabolism of muscle proteins by enzymes activated by inactivity. Joint stiffness and loss of capsular compliance begin soon after immobilization. The risk of thromboembolic event, pulmonary atelectasis, and pressure ulcers rises along with inactivity.

When bed rest is prescribed for acute lumbosacral injury, the aforementioned complications are risked. Bed rest in acute low back pain is not associated with either quicker resolution of pain or return to regular activity. Regular activity as tolerated maximizes the return to function and decreases patient pain score report.

Pharmacological

Nonopiate Analgesics

For most patients with low back pain, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line pharmacological treatment. Acetaminophen is recommended by the American Pain Society and American College of Physicians as the initial pharmacological treatment of nonspecific back pain due to its record of safety in other settings of musculoskeletal pain. Acetaminophen carries a low risk of harm; it is not associated with the risk of either gastrointestinal bleeding or myocardial infarction and is relatively well tolerated [34]. Hepatotoxicity may be seen at doses approaching the recommended maximum daily allowance (3 g/day), and so caution must be taken in those patients with preexisting liver conditions or heavy alcohol use.

NSAIDs exert their anti-inflammatory, analgesic, and antipyretic effects via the inhibition of the cyclooxygenase (COX)-2 enzyme. Nonselective NSAIDs (celecoxib) also inhibit COX-1, which is responsible for gastric mucosal protection via prostaglandin production. A review of different NSAID formulations indicates similar efficacy when compared to placebo in acute and chronic back pain and similar intrafamily efficacy. Thus, treatment decisions may rely on side effect profile, prior response to NSAIDs, cost, and dosing schedule. Each member of the class is associated with gastrointestinal and renal adverse effects, including gastrointestinal ulcers, hemorrhage, and perforation, as well as decreased glomerular filtration. A 2006 meta-analysis of 138 individual studies revealed an approximate twofold class-wide risk elevation in myocardial infarction when compared to placebo, except naproxen, which showed no such increased risk. Cardiovascular, gastrointestinal, and renal risks should be taken into account prior to prescribing or recommending NSAIDs for nonspecific low back pain. The long-term use of NSAIDs may be combined with misoprostol, a prostaglandin that decreases the risk of gastrointestinal ulceration, or a proton pump inhibitor [34].

Opiate Receptor Agonists

There exists significant controversy regarding the use of opiate receptor agonist medication in low back pain. Opiate receptors are widely distributed throughout the brain, spinal cord, and intestinal tract and are activated by morphine and its derivatives and homologues. While considered the strongest class of pain relievers, they carry significant potential for dependence and abuse due to their effects on the dopaminergic reward system of the brain. In 2009, the American Pain Society and the American Academy of Pain Medicine published joint guidelines on the use of opioids for chronic noncancer pain to aid practitioners in decisions regarding this class of medication [35]. Primary among these recommendations include time-limited rather than symptom-limited course of medication. Common adverse effects

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include constipation, nausea, somnolence, and pruritus.

Tramadol is a synthetic agent with weak affinity for the α-opiate receptor. Clinically, it has greater efficacy than NSAIDs and is relatively comparable to weak opiates [35]. Tramadol has similar adverse effect tolerability to acetaminophen-opioid combinations; however, it has been linked to the serotonin syndrome when used in combination with serotonin receptor antagonists.

Skeletal Muscle Relaxants

Medicines known as "skeletal muscle relaxants" are related neither pharmacologically nor structurally. Those commonly used for the relief of musculoskeletal spasticity are baclofen, carisoprodol, cyclobenzaprine, metaxalone, methocarbamol, tizanidine, and orphenadrine. It is unclear if these medications work to relax muscles or if their effects stem mostly from sedation [34]. Medications in this grouping have been shown to demonstrate short-term pain relief for acute low back pain, but no agent has been shown to be more effective than others [36]. These medications carry a high rate of adverse side effects, and sedation commonly limits their use. Several studies have indicated the equivalence of benzodiazepines when compared to skeletal muscle relaxants for acute low back pain, suggesting similar benefit. All medications here referenced may be more effective when combined with an NSAID or acetaminophen [36].

Antidepressants

Certain antidepressants with noradrenergic antagonist activity may have pain-modulating properties independent from their effects on mood disorders. Tricyclic antidepressants (TCAs) such as amitriptyline have long been used in chronic pain conditions, and, in recent years, serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, venlafaxine, desvenlafaxine, and others carry similar indications. TCAs show small benefit over placebo for chronic nonspecific pain in some meta-analyses, while SNRIs have shown benefits for certain types of chronic pain. High rates of adverse effects limit the use of these medications and prevent their use as a first-line treatment [36].

Systemic Corticosteroids

While it has been suggested that the inflammatory response associated with extruded intervertebral disk nuclear material may be stemmed with oral corticosteroids, several studies in the setting of lumbar radicular pain have demonstrated no improvement versus placebo. Similarly, despite the euphoric effect achieved by some patients, these medications are also without effect in nonspecific acute low back pain [34].

Disease-Modifying Antirheumatic Drugs (DMARDs)

There is no role for antitumor necrosis factor (TNF)-α biologic therapy in the treatment of nonspecific low back pain [34].

Exercise

Whether done in the home setting or under the guidance of a physical therapist, stretching, and strengthening activities are commonly prescribed for acute nonspecific back pain. A meta-analysis of 11 studies utilizing the McKenzie (directional preference) method indicated significant improvement in pain and disability after 1 week of therapy [37], resulting in a recommendation for usage [strength of recommendation taxonomy (SORT) B]. Evidence suggests that there is a mild benefit for exercise protocols in chronic nonspecific back pain and little to no improvement when compared to other treatments in acute back pain [38].

Back School

Education is commonly utilized in the treatment of low back pain; it is apparent, however, that there is little to no standardization on what constitutes back school curriculum, and thus, these approaches vary widely. A 2016 review analyzed 273 trials that studied the effects of back schools on nonspecific low back pain; four were deemed to be rigorous enough to meet inclusion criteria. Given the paucity of high-quality evidence available, the authors were unable to comment on the efficacy of back schools for acute and subacute nonspecific LBP [39].

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Psychological Intervention

Cognitive-behavioral therapy (CBT) is a method of psychotherapy that attempts changing cognitive processes to affect changes in behavior, thought, and emotional responses. CBT has been applied to chronic pain settings with varying results. In the setting of chronic pain, CBT has improved pain experience, positive coping, and social role function when compared to placebo or other treatments [40].

Spinal Manipulation

A 2004 Cochrane meta-analysis concluded that spinal manipulation was superior only to sham treatments and inert interventions. It demonstrated no advantage over "usual care," analgesic medication, physical therapy, exercise, or back school. Chronic pain applications were found to yield similar results. These results were unaffected by the presence of pain radiation, study quality, manipulator, nor therapy combinations [41].

Acupuncture

A Cochrane review of studies investigating the use of acupuncture in the treatment of low back pain found acupuncture to be effective for pain relief and equivalent to other complementary or conventional treatments. For short-term relief of chronic pain, acupuncture was more effective than sham procedure and placebo. Data regarding the effects on short-term low back pain were inconclusive [42].

Epidural Steroid Injection

The use of epidural steroid injections in the treatment of pain for lumbar radiculopathies as well as spinal stenosis is increasing. A meta-analysis of 38 placebo-controlled trials evaluating the effect of epidural steroid injection in lumbar radiculopathy and spinal stenosis showed brief and nonsustained effects of injection in lumbar radiculopathy that were below predefined set points for clinical significance. There were no effects in spinal stenosis. Neither patient characteristics nor technical factors had an effect on these results [43].

Surgery

Evidence is very clear that there are limited roles for surgery of the spine outside the conditions of sciatica, pseudoclaudication, or spondylolisthesis [44]. Prolonged or worsening neurological symptoms in the setting of diagnosed disk disease unresponsive to or inappropriate for ESI should stimulate referral for surgical evaluation.

Lumbar diskectomy is the most common operation in the United States for reasons related to disk herniation, but there remains poor evidence supporting its use when compared to conservative treatments. Newer treatments in minimally invasive spine surgery (MISS) offer lower perioperative morbidity to patients.

The largest and longest-term comparison between nonsurgical and surgical approaches was published as the 10-year follow-up to the Maine lumbar spine study ($n = 400$) [44]. Ten years after initial presentation, postsurgical patients were more likely to be satisfied with their current condition when compared to the medically managed patients (71% vs. 56%, $P = 0.002$), whereas there was insignificant difference between the two groups with regard to improvement in the initial presenting symptom and work and disability status [44].

Chronic Low Back Pain

Low back pain of greater than 6 months duration develops in a small percentage of patients. These conditions carry a very low likelihood of a specific diagnosis, and symptomatic cure is unlikely. Treatment should be supportive, with efforts aimed at improving pain and function. While the mechanisms of initial injury and chronic pain propagation are unclear, it is proposed that these disorders are primarily mechanically induced, and then maladaptive physical and cognitive compensations produce a mechanism for an ongoing pain.

A recent systematic review demonstrated predictors favoring persistent disabling back pain: maladaptive coping behaviors, nonorganic signs, functional impairment, significant comorbidities, and psychiatric comorbidities. Factors such as low

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level of fear avoidance and functional impairment predict recovery at 1-year time [45].

The transition from acute to subacute to chronic pain appears to be one strongly mediated by psychosocial factors rather than anatomic or disease-based factors. Therefore, interventions attempting to prevent chronicity transformation have utilized psychological approaches.

Disorders of the Neck

Cervical Radiculopathy

General Principles

A common cause of neck pain is impingement of the cervical nerve roots exiting the spine. This is frequently caused by disk pathology, facet joint osteophytes, or degenerative disk disease, further affected by intraneural edema or inflammatory mediators such as substance P. The annual incidence of cervical radiculopathy has been found to be 83 in 100,000 persons [22].

The nomenclature of the cervical nerve roots differs from that elsewhere in the spine. The presence of an eighth cervical nerve root determines that most cervical nerve roots exit the spinal canal superior to their correspondingly named vertebra; the C7 nerve root exits at the level of the C6–C7 intervertebral disk. The exception to this rule is the eighth cervical nerve root, which exits between the C7 and T1 vertebral levels. The most commonly affected nerve root is the C7 root, which is impinged at the level of the C6–C7 intervertebral disk.

Presentation

When compared to chronic spondylosis of the cervical spine, pain associated with radiculopathy is more commonly unilateral [46]. The most common mechanism of acute cervical radiculopathy is that of annular failure of the intervertebral disk resulting in disk deformation or frank extrusion of nuclear material. Chronic radicular symptoms, which may persist in up to two thirds of patients, are more commonly associated with chronic spondylosis, usually characterized by facet joint osteophytosis or disk degeneration [22].

As with lumbar radiculopathy, the clinical presentation is highly dependent on the exact impinged nerve root or roots; however, clinical and symptom overlap does occur. Pain in proximal nerve root distribution is accompanied by distal distribution neuropathy (paresthesias or other sensory dysfunction). Commonly, referred pain from unilateral cervical radiculopathy is vaguely localized to the ipsilateral neck, shoulder, or medial scapular border [46], whereas radicular pain may follow a dermatomal distribution.

On physical examination, pain is usually exacerbated by neck extension as well as neck rotation toward a patient's symptomatic side, which narrows the neural foramen (Spurling's sign). Conversely, a patient may find mild relief with neck flexion, shoulder abduction, and scapular retraction. Altered deep tendon reflexes corresponding to the affected nerve root may be present. Upper motor neuron findings such as hyperreflexia, clonus, and Hoffman's sign should be absent: their presence should stimulate search for myelopathic conditions.

Diagnosis

The differential diagnosis of cervical radiculopathy encompasses pathologies of the neck, shoulder, viscera, and extremities. Thus, trauma, myelopathy, degenerative spondylosis, rotator cuff pathology, myocardial ischemia, zoster, and other conditions should be considered at differential diagnosis [46]. As noted with lumbar radiculopathy, plain-film x-ray is of limited use, given the poor correlation between findings and the patient's report of symptoms. Similarly, in the absence of certain findings suggesting cancer, myelopathy, or acute pathologies, it is recommended that practitioners delay advanced imaging until after a suitable period of conservative treatment has failed [47]. MRI or CT are best utilized as a confirmatory test of nerve root compromise, in anticipation of referral to spine subspecialist and possible interventional treatment, with limited evidence available to recommend for or against the use of electromyography (EMG) [47].

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Management

The prognosis of cervical radiculopathy is optimistic and well described [26, 46]. The majority of patients will improve over time, with 75–90% having no or minimal further sequelae. Management decisions must be made with reference to this high rate of recovery.

The following interventions have insufficient evidence to recommend or discourage their use: medication, physical therapy, traction, cervical manipulation, and cervical collar. Several of these have demonstrated improvement in patients' symptoms in uncontrolled trials. Cervical manipulation has been rarely associated with emergent vascular and nonvascular complications then requiring definitive surgical treatment [47]. Similar consideration should be used when applying pharmacological treatments to cervical radiculopathy as were discussed with regard to lumbar radiculopathy.

Injection of an anti-inflammatory steroid and anesthetic mixture into the epidural space may provide symptom relief for up to 60% of patients and delay or negate the need for surgery in an additional 25% [47]. Rare but potential complications such as spinal cord damage and death may be considered when developing an interventional treatment plan for those patients with cervical radiculopathy.

Surgical referral is appropriate in individuals who have documented cervical radicular symptoms that are intolerable and resistant to a prolonged (6 weeks) course of conservative treatment.

Acute Cervical Strain

General Principles

The acute cervical strain caused by acceleration-deceleration and subsequent energy transfer to the neck is known as whiplash. It commonly occurs during motor vehicle accidents, but also during sporting activities. It may result in a variety of bony and soft tissue injuries, manifest by myriad symptoms. This constellation is known as whiplash-associated disorders (WAD) [48]. These conditions generally have a positive prognosis, with 87% and 97% cited as having recovered from their injuries at 6 and 12 months; however, this optimism is debated [48].

Presentation

Common symptoms after motor vehicle accident (MVA) are neck pain (88–100%) and headache (54–66%), but also commonly seen are neck stiffness, shoulder pain, arm pain or numbness, and others [48]. As in other injuries of the axial spine, issues surrounding the compensation for injury and work delay clinical improvement. In 2001, Côté reviewed a Canadian study investigating the association between insurance systems and claim-closure and compensation times after WAD. In the no-fault province of Quebec, the median claim-closure time was 30 days and 4.1% of claimants were still compensated at 1 year. In Saskatchewan under the tort system, the median claim-closure time was 433 days and 57% were still compensated at 1 year, implying extra-physiological influences to recovery [49].

Diagnosis

An acute cervical injury in the setting of an appropriate mechanism of injury is suitable for the diagnosis of whiplash-associated disorders. Care must be taken not to overlook other conditions that can be present with cervical and cranial trauma, such as fracture, intracranial hemorrhage, mild traumatic brain injury (mTBI), and others. Typically, diagnostic testing and imaging are only utilized to exclude these other conditions.

Management

Management of whiplash should be multimodal and include an assessment of psychological wellness in accordance with the biopsychosocial model. Patients' beliefs, coping strategies, locus of control, and disability should also be measured [48]. It has been suggested that active interventions may be more effective in those with WAD. These have been shown to be beneficially long term on pain, global perceived effort, or participation in daily activities [48]. Patients should be educated and reassured regarding the positive prognosis. Active therapy for comorbid mood disorders should be addressed immediately.

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Return-to-clinic and emergency room visit criteria should be discussed. If applicable, continuing care of mTBI should be provided.

Prognosis

The prognosis of acute whiplash is favorable for most individuals. Age, gender, baseline neck pain, baseline headache, and radicular complaints all have independent influence on recovery. It is well recognized that nonmedical factors may also strongly affect recovery. The above Canadian study further noted that when Saskatchewan changed its insurance systems from tort to no-fault, it achieved a 54% reduction in median time to claim closure [49]. The influence of jurisdiction on recovery is further highlighted by chronic whiplash, which is low in historically no-fault provinces (Québec), less litigious countries (Greece), and where whiplash is not compensated (Lithuania) [49].

Cervical Myelopathy

General Principles

Chronic atraumatic compression of the cervical spinal cord due to spondylosis is the most common cause of spinal cord compression in the world [50]. It is understood that 40–60% of untreated cervical spondylotic myelopathy (CSM) cases will progress with worsening neuropathy, neuroinflammation, and apoptosis. Radiographic evidence of cervical stenosis is insufficient to produce the syndrome, as some patients with significant stenosis never develop myelopathy for reasons that are unclear.

Presentation

The clinical presentation in CSM varies greatly, depending on the site and type of lesion and whether it produces motor or sensory and upper motor neuron or lower motor neuron signs in the upper or lower limbs [50]. Onset is typically between ages 50 and 70, of insidious onset and progressive and unremitting. These characteristics may help distinguish it from other neuropathic syndromes, such as peripheral compression or multiple sclerosis.

Symptoms may include neck and/or upper limb pain, weakness, numbness or loss of sensation in the upper or lower extremities, and bladder symptoms such as incontinence or urinary frequency.

Physical exam may reveal signs consistent with upper motor neuron dysfunction: hyperreflexia and/or clonus, Hoffman's sign, Babinski's reflex, multilevel nerve root weakness, sensory loss, or signs of spasticity in the lower limbs [50].

Diagnosis

Plain-film x-ray is commonly obtained in individuals with CSM. With the advent of cross-sectional imaging, however, MRI and intrathecal enhanced CT (CT myelography) have become the studies of choice to evaluate this condition [50], as they are able to aid in the calculation of intracanalar dimensions. The role of EMG is to evaluate for the presence of other conditions that may mimic the findings of CSM, such as peripheral compressive lesions. Cerebrospinal fluid and blood analysis may be used to similarly exclude other neurological conditions [50].

Management

Myelopathy is a progressive disorder and little evidence exists that nonoperative treatment halts or reverses its progress. Thus, nonoperative treatment (intermittent bed rest, the use of collar, anti-inflammatory medication, and discouragement of high-risk activities) is reserved only for asymptomatic patients or those with mild symptoms [50]. Referral or comanagement with a neurologist or neurosurgeon is recommended. For individuals with moderate to severe or rapidly progressive myelopathic symptoms, immediate surgical referral is warranted.

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Disorders of the Upper Extremity 115

Christopher Jensen

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Hand and Wrist

Infectious and Inflammatory

Paronychia

Paronychia refers to an inflammatory process of the tissues of the lateral nail fold, frequently following minor trauma. This response is subdivided into acute (<6 weeks) and chronic (>6 weeks).

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Typical presentation consists of erythema, swelling, and tenderness of the affected area. As with most soft tissue infectious, treatment must follow evaluation to exclude abscess formation. In the absence of an abscess, treatment consists of soaking in warm water or antiseptic with application of topical antibiotic; severe cases or cases which fail to respond to this may require systemic antibiotic therapy. If oral antibiotics are considered, risk factors for MRSA (incarceration, hospitalization, or known colonization) should dictate therapy. If there is known exposure to oral flora as in patients prone to nail chewing or dental work, Augmentin is ideal.

In the event of abscess formation, incision and drainage (I&D) should be performed. Digital block can provide excellent anesthesia for the procedure after which an 11 blade may be run parallel to the nail on the affected side to allow for drainage of purulent material. Warm soaks should be maintained after I&D to facilitate ongoing drainage, and in most cases, antibiotic therapy is not needed following the procedure [13].

Felon

Infection of the soft tissue (pulp) of the fingertip is referred to as a felon and commonly arises from either a puncture wound of the fingertip or spread of infection from an untreated paronychial infection. This typically presents as a painful red swollen fingertip, but importantly this should not extend proximal to the distal interphalangeal (DIP) joint as the septated compartments of the digital pulp confine the spread of the infection. Evaluation for the presence of abscess is critical in determining the necessary course of treatment and is most easily done through soft tissue ultrasound of the area. The presence of abscess mandates incision and drainage and in many cases operative intervention. Regardless of the presence of abscess, patients should undergo antibiotic therapy including staphylococcal and streptococcal coverage which can be further guided by culture obtained during I&D.

Herpetic Whitlow

Herpetic whitlow is a viral infection of the distal finger which can be caused by human herpes virus 1 or 2. This commonly presents as one or more vesicular lesions, but importantly the pulp space is not directly involved, and therefore on examination the fingertip should not be tense. Distinction of this from a felon is important as drainage of the lesions of whitlow should be avoided if possible; incision and drainage may result in spread of the virus and increase the chance of secondary bacterial infection. If the diagnosis is in doubt, confirmation can be obtained through viral culture, Tzanck smear, or antigen testing of fluid from a lesion. The condition is self-limited with typical resolution within 2–3 weeks though recurrence is common, present in between 20% and 50% of patients. Treatment primarily consists of symptomatic management with anti-inflammatories and elevation of the affected region. Limited evidence suggests chronic acyclovir may reduce the rates of recurrence [17].

Tenosynovitis

Infectious tenosynovitis represents an inflammatory response within the tendon and its surrounding synovial sheath. This is most commonly the result of local penetrating trauma but can, in rare cases, be the result of hematogenous seeding. While this can occur in any tendon sheath and associated synovium, the most common site is in the hand and wrist and is subdivided into flexor and extensor disease. Flexor tenosynovitis presents with four key features (Table 1), while extensor disease can present much more subtly than its flexor counterpart. Typical presentation consists of local redness and tenderness, most often of the wrist. A high degree of suspicion should therefore be maintained in dorsal wrist cellulitis, especially if the patient's response to antibiotic therapy is poor [3].

Treatment of the infection is guided by the severity of presentation. Hospital admission with intravenous antibiotic therapy is advised with specific coverage tailored to the mechanism of exposure. Bite wounds should be treated based on the oral flora of the offending creature; water exposure should cause consideration of pseudomonal coverage. Early evaluation by an orthopedic surgeon is advisable as irrigation, open washout, and serial debridement can be required to clear the infection.

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Table 1 Knavel's signs – in combination, these have been shown to have sensitivity of greater than 90% for pyogenic tenosynovitis. Specificity is significantly lower (approximately 50%). Other considerations should include palmar abscess or (in patients who are anticoagulated) hemorrhage [10]

Sign	Sensitivity	Specificity
The affected finger is held in slight flexion	91.4%	51.3
The affected tendon displays fusiform swelling	94.3	51.3
The affected tendon is tender to palpation	91.4	69.2
Passively extending the involved digit produces pain	97.1	53.8



Fig. 1 The Finklestein test is performed by having the patient grasp their thumb within their other digits. The examiner then applies ulnar force to the hand. A positive test consists of significant pain at the radial styloid

De Quervain's Tenosynovitis

Atraumatic radial wrist pain can indicate inflammatory change in the extensor pollicis brevis or abductor pollicis longus tendons, commonly called De Quervain's tendinopathy. This is thought to be an overuse injury though etiology is not fully understood. Diagnosis is suggested by a positive Finkelstein's test (see Fig. 1). In mild cases, immobilization with a thumb spica splint can be performed. In severe cases or when a patient is suffering disability, treatment may be attempted with glucocorticoid injection between the two tendons. In the event a patient's symptoms are refractory to both, surgical evaluation may be considered.

Intersection Syndrome

Commonly mistaken for De Quervain's tendonitis, intersection syndrome presents similarly with pain in the dorsal and thenar wrist but can be distinguished by pain located more proximally and dorsally as opposed to over the radial styloid as seen in De Quervain's. Treatment consists of activity modification through reduction use of wrist extensors. If that fails local steroid injection where the first and second dorsal compartments cross can be considered, ideally under ultrasound guidance.

Traumatic

Mallet Finger

This injury consists of a tear of the extensor tendon at the DIP joint, most often due to sudden forced flexion of the extended joint against resistance. The result is a tendon which may be abnormally stretched, torn, or avulsed from the distal phalanx. Patients present with a DIP joint which can be passively extended but is unable to be extended actively. In rare cases patients may have limitation in passive extension which, if present, should raise the concern for debris from the injury trapped in the joint space. If found this merits further evaluation and possible surgical intervention. In its absence, treatment consists of rigid adherence to splinting of the DIP joint in full extension for 6 weeks. Extension must be maintained during this time, and the patient should be advised that the digit should be held in extension manually during any periods when the splint is removed or exchanged.

Jersey Finger

Forced extension of the DIP joint against resistance can result in damage to the flexor digitorum profundus tendon. This will typically present with volar DIP pain and a finger which is held in extension at rest. There may or may not be a palpable volar mass along the normal course of the tendon representing the torn and retracted

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tendon. The examiner will commonly find a DIP joint in which active flexion is weak (partial tear) or absent (complete tear) when the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint are held in extension. Management of jersey finger is surgical, and prompt referral to an orthopedic hand surgeon is warranted in all cases to limit disability. In the interim, the DIP joint should be splinted in partial flexion.

Central Slip Extensor Tendon Injury

Forced flexion of the PIP joint from an extended position can result in a tear of the central slip of the extensor tendon. This allows the lateral bands to displace around the joint in the volar direction. The characteristic deformity which develops consists of a PIP joint which is flexed with concurrent hyperextension of the DIP joint, referred to as a boutonnière deformity though this can develop gradually and will frequently be absent on initial presentation. Treatment for the injury is extension splinting of the PIP joint continuously for 6 weeks.

Scaphoid Fracture

The scaphoid is both the largest carpal bone and the most likely to sustain fracture, most often with forced wrist extension or axial compression such as sustained in a fall onto an outstretched hand. Patients generally present with radial wrist pain, immediately proximal to the first metacarpal, frequently accompanied by reduced grip strength. Classically tenderness is expected in the anatomic snuffbox but may also be present distal to Lister's tubercle or along the dorsal wrist crease. Plain films of the wrist are the initial radiographic study and should include a dedicated scaphoid view. The physician should however be aware that acute fractures have a false-negative rate reported as at least 20%. If suspicion remains high, following a negative radiograph, acute MRI, or, if not available, CT can clarify the diagnosis. In the event, advanced imaging is delayed in a patient with suspicious presentation; the patient should be placed in a thumb spica splint.

If a scaphoid fracture is found, surgical evaluation is mandated if there is any evidence of instability. This includes fractures of the proximal pole, displacement of more than 1 mm, comminuted fractures, or unstable fractures of any other carpal bones. As the potential for disability in cases of non-union is high, referral may be considered even in the absence of these signs or if the patient's circumstances would benefit from a more rapid return to work or sport.

Hamate Fracture

Much like a scaphoid fracture, hamate fractures will commonly result from a fall on an outstretched hand but are also common with a direct impact injury to the palm of the hand from a bat, club or racquet in sports. The area of maximum tenderness is generally the hypothenar eminence but can be more diffuse. The hook of hamate pull test can help confirm the diagnosis (see Fig. 2). Initial imaging is by plain film, but sensitivity of this is low and if negative advanced imaging with CT should be considered. In the event of a fracture, there can be concurrent injury to both the ulnar nerve and artery, so assessment for sensory loss and Allen's test for arterial patency should be performed. If neurovascular compromise is present, the patient should undergo urgent surgical evaluation. If no surgical intervention is required, the patient should be placed in a short-arm cast. If swelling is significant at time of

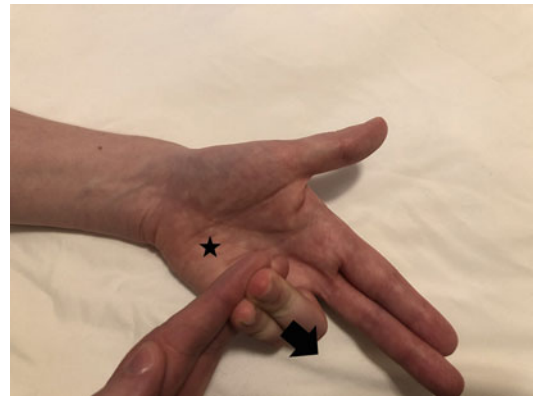


Fig. 2 The hook of hamate pull test is performed with the patient flexing the last two digits with the wrist in ulnar deviation The examiner then attempts to extend the fingers against resistance. A positive test consists of pain in the region of the hamate (*)

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presentation, a volar splint may be used as initial therapy.

Elbow

Radial Head Subluxation

Classically referred to as nursemaid's elbow, this is a common injury in children under 5 in which the annular ligament slips over the head of the radius. This is commonly caused by traction on the forearm, typically with the hand pronated. Most often parents report a recent history of non-use of the affected extremity, and the patient typically does not have significant discomfort so long as the arm is not manipulated. X-ray may be used if the diagnosis is in doubt but should not be relied on as positioning for the film can cause reduction of the displacement. Multiple maneuvers have been suggested to reduce the subluxation with the highest rate of success found on hyperpronation of the affected extremity. The physician should hold the affected elbow in one hand, applying pressure medially to the radial head. The other hand can then be used to hyperpronate the hand. If the patient is not using the arm within 30 min of reduction, further evaluation for additional injury to the elbow including radiographic exam should be considered.

Olecranon Bursitis

Bursitis can develop as the result of prolonged pressure, injury, infection, or other inflammatory insult. In the olecranon this acutely presents as warm painful swelling of the elbow. Of note, unlike an effusion or infection of the elbow joint itself, extension should not exacerbate pain in bursitis. The diagnosis can be made clinically; however if the physician suspects infection or crystalline etiology, the bursa may be aspirated. If this is done, following the procedure the area should be compressed as it will, in the majority of cases, reaccumulate. Treatment of non-infectious bursitis consists of protecting the bursa from ongoing trauma and compression to prevent fluid reaccumulation. If allowed to persist chronically, the bursal sac may thicken and require surgical intervention to correct.

Lateral Epicondylitis

Classically referred to as tennis elbow, this is an overuse injury causing degenerative change in the extensor carpi radialis brevis (ECRB) tendon as it inserts into the lateral epicondyle. Typical presentation is pain just distal to the lateral epicondyle, which on exam can be aggravated by extension of the wrist against resistance [8]. Multiple therapies have been advocated to treat the condition including counter-force bracing, eccentric exercise programs, and injections of steroids or prolotherapy using injections of glucose or platelet-rich plasma, but evidence for clear efficacy of any of the techniques is lacking [2].

Medial Epicondylitis

Similar in both mechanism and presentation to lateral epicondylitis, this condition is a degenerative injury of the flexor mechanism of the wrist as it inserts into the medial epicondyle. Pain is typically present at and just distal to the medial epicondyle and is exacerbated by flexion of the wrist against resistance. As with lateral epicondylitis, multiple therapies are recommended, and evidence for their efficacy is not compelling.

Arm

Humeral Fractures

Supracondylar Fracture

Supracondylar fractures are the most common elbow fracture in pediatric populations and are significant both due to the technique used in proper imaging and the potential for neurovascular compromise. Patients typically present with elbow pain, swelling, and significantly reduced ROM at the elbow following a fall onto

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an outstretched hand. Adequate analgesia should be given immediately to facilitate a high-quality neurovascular examination. In cases with visible deformity, splinting should be considered prior to radiographic examination as repositioning of the extremity may cause further neurovascular injury. Orthopedic consultation is warranted in most cases though a posterior splint and sling may be considered if the fracture is nondisplaced and the patient is neurovascularly intact [4].

Mid-Shaft Humeral Fracture

Mid-shaft fractures will most frequently occur from a direct impact of the humerus but should also be considered in cases of pain after rapid contraction of the musculature of the arm such as with throwing or arm wrestling. Patients typically present with local tenderness, frequently with associated bruising. The examiner should take care to perform a thorough neurovascular examination including ulnar, radial, and median nerve as radial nerve runs adjacent to the bone in this area. If any neurovascular compromise is found, emergent evaluation by an orthopedic specialist is indicated. Most other cases are treated non-operatively, but as functional bracing is frequently required for optimal outcomes, orthopedic evaluation is generally warranted.

Proximal Humeral Fracture

Proximal injuries of the humerus typically require high-energy collisions in the young population (sports or motor vehicle crashes) but can occur with low-energy falls in the over 50 population. Evidence supports that non-displaced fractures can be treated non-operatively with a sling [6] and there is increasing evidence [12] that injuries with a single displaced fragment may be as well, however at this time the majority of cases with any displaced fragments warrant orthopedic evaluation.

Bicep Tears

Acute Tear of the Long Head of the Proximal Bicep

Injury to the long head of the biceps tendon will most frequently present following an acute injury with patients frequently reporting an audible pop associated with onset of pain. The pain itself is generally described as radiating distally from the anterior shoulder and is exacerbated by flexion or supination of the forearm. This may be accompanied by a visible deformity in which the shortening of the muscle belly causes a localized bulge along the humerus though this can be subtle in patients with obesity [19]. The examiner will frequently note localized tenderness in the bicipital groove and, if the patient presents acutely, swelling and bruising of the proximal arm. Therapy is generally conservative as rupture of the long head is associated with only mild to moderate loss of strength but in patients who rely on physical strength or find the cosmetic result of the tear unacceptable surgical intervention is reasonable.

Acute Tear of the Distal Bicep

Distal bicep tears will typically present with acute pain in the anticubital fossa following injury. Bruising may be present acutely but visible muscular deformity is rare. Patients are expected to have increased pain and weakness with resisted flexion or supination at the elbow. The diagnosis can be further suggested by the squeeze test, a lack of forearm motion with compression of the bicep, or the hook test (see Fig. 3). The diagnosis is confirmed through the use of musculoskeletal ultrasound or MRI. All patients with a distal tear should undergo orthopedic evaluation as delayed intervention is associated with worsened functional outcomes

Shoulder

Glenohumeral Dislocation

Anterior Glenohumeral Dislocation

The vast majority (>95%) of shoulder dislocations occur anteriorly. Patients will typically present following an impact to an abducted externally rotated arm which forces the head of the humerus to move anteriorly but can uncommonly occur as the result of a fall onto the arm or direct impact from behind. Patients will typically present with decreased and painful range of motion in the

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Fig. 3 The hook test is performed with the patient's hand in supination. The examiner slides his finger behind and then pulls forward on lateral aspect of the distal bicep tendon. Inability to grasp the tendon suggests a complete distal bicep tear

shoulder and will frequently have a visible or palpable deformity of the joint. In comparison with the patient's other shoulder, the examiner may note a more flattened appearance as the humeral head shifts anteriorly and inferiorly. This shift can cause injury to the axillary nerve or rotator cuff. The former is most easily assessed through sensory evaluation of the proximal third of the affected arm, while the latter is discussed later. Assessment of distal pulses allows for evaluation of axillary arterial damage. Multiple techniques are described to reduce an anterior dislocation, and most are beyond the scope of this text, but the Stimson technique bears mentioning as it has a high rate of success and can be performed without a skilled assistant. To perform this, the patient is positioned prone on a gurney with the dislocated shoulder dangling. 20–30 lb of weight are suspended from the affected arm, and the shoulder is allowed to passively relocate. The patient is sedated and allowed to rest in this position; >90% of dislocations reduce within 30 min [11].

Posterior Glenohumeral Dislocation

Posterior dislocation are a rare injury which can occur following direct impact to the anterior shoulder but should also be considered in cases where the patient has undergone violent muscle contractions as in cases of seizure or electrical shock. Patients generally present with inability to externally rotate a painful arm and may demonstrate a visibly flattened anterior shoulder with visible or palpable posterior displacement of the humeral head. Reduction is performed with the arm held in adduction with elbow bent. A sheet is hooked over the forearm and used to apply axial traction downward. Success rates vary but are reduced with duration and extent of dislocation

Inferior Glenohumeral Dislocation

Inferior dislocations most commonly occur following an impulse applied to a maximally abducted arm as in a patient who grasps an overhead object while falling. Patients present with an arm which is held in maximal abduction and cannot be adducted. Despite its rarity this injury merits discussion as it is associated with high rates of injury to adjacent structures making a thorough neurovascular evaluation critical. Reduction is performed through traction directed axially along the humerus. An assistant is frequently required to hold the patient in place as traction is applied

Imaging. In patients with suspected glenohumeral dislocation, pre- and post-reduction radiographs allow for confirmation of the diagnosis, successful reduction, and assessment for any associated bony injuries. These should include the traditional AP and axillary view but also a scapular "Y" view. If plain films are inconclusive but posterior dislocation is strongly suspected, subsequent CT scan may improve sensitivity of the evaluation. If imaging demonstrates that the reduction has failed, orthopedic intervention and open reduction may be required.

Aftercare. Following reduction, neurovascular evaluation should be repeated to assess for any damage done in the course of reduction. Patients

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are then immobilized using a sling, traditionally for 3 weeks though there is evidence for reduced loss of range of motion with only 1 week of immobilization in patients over 30. Regardless of age patients should be instructed to maintain passive range of motion in the affected arm through pendulum swings during the period of immobility. Following this physical therapy may be useful in regaining lost range of motion and preventing redislocation.

Rotator Cuff Injuries

Presentation. The presentation of patients with rotator cuff tears is variable but generally includes pain which is exacerbated with overhead motion. Onset typically follows trauma or repetitive strain in young populations but as patients age may be subtle and atraumatic. A number of exam maneuvers have been proposed to aid in diagnosis of tears, but evidence that the location of pain on physical examination can localize the injury is poor [7]. Injury of the cuff as a whole is suggested by inability to smoothly adduct the arm from overhead to the side or by evidence of shoulder impingement. This can be demonstrated by the Hawkins-Kennedy or Neer's tests (Figs. 4 and 5, respectively)

Imaging. Imaging studies can be used for confirmation of cuff injury. Plain film has limited value but does suggest the diagnosis if the humeral head is found to be displaced [9]. In the hands of a skilled operator, ultrasound has been demonstrated to be accurate in the diagnosis of tears, but MRI appears to be more accurate in gauging the extent of a tear and degree of tendon retraction [16].

Treatment. It is classically believed that the majority of patients are able to be treated conservatively with physical therapy, but key exceptions which are worth noting include patients who have had an acute or acute on chronic full thickness tears which result in significant loss of function. Within that population patient outcomes following acute surgical intervention have been shown to be improved. Of note, recent data does suggest that even patients exhibiting small tears may have improved functional outcomes following surgical intervention [14].



Fig. 4 To perform the Hawkins-Kennedy test, the patient flexes the elbow and shoulder to 90 degrees. The examiner then applies downward force to the hand while stabilizing the upper extremity proximal to the elbow. Pain in the shoulder region suggests shoulder impingement



Fig. 5 Neer's maneuver is performed by passively flexing the shoulder while using the other hand to prevent the patient from shrugging. Pain suggests shoulder impingement

Subacromial Bursitis

The subacromial bursa lies between the rotator cuff and the acromion and is frequently inflamed by any of the processes above but can also arise from systemic inflammatory disease. Typical patients will present pain of the proximal third of the lateral arm of the affected side. Unlike a rotator cuff tear which can present with very similar pain, bursitis should, in theory, not cause a lack of

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strength; however guarding on the part of the patient may make this distinction difficult in practice. Steroid injection into the bursa can be useful both diagnostically and therapeutically as a full return to baseline following injection makes other shoulder pathology unlikely. Even with full pain relief, physical therapy can be an important adjunctive therapy to prevent recurrence.

Frozen Shoulder

Frozen shoulder or adhesive capsulitis is a poorly understood condition which manifests as gradual and progressive limitation in active and passive range of motion. It typically presents in the 50s and 60s with onset more common in patients with comorbidities, most prominently diabetes. Examination is expected to show reduction in active and passive range of motion, frequently with associated pain. In contrast to subacromial bursitis, steroid injection is not expected to relieve this discomfort. The utility of imaging is mostly in exclusion of alternative diagnoses, with X-ray findings limited to at most osteopenia. MRI may be considered but will generally be expected to demonstrate only capsular thickening. Treatment is controversial and poorly supported by evidence but will frequently include range of motion exercises and potentially glucocorticoid injection. If the patient fails to demonstrate improvement, orthopedic consultation may be helpful [5].

Clavicular Fracture

A fracture of the clavicle can commonly occur following a fall on an outstretched arm or direct trauma to the bone. Patients typically present with localized point tenderness, often with associated visible deformity which can result from bony displacement or hematoma formation.

Mid-Shaft Clavicle Fracture

The vast majority of clavicle injuries (70–80%) occur mid-shaft and shortening, and displacement is common. Evaluation should include neurovascular exam of the extremity and assessment for underlying injury to the lung and pleura. X-ray is generally sufficient to confirm the diagnosis. Indications for orthopedic evaluation of mid-shaft fractures include evidence of neurovascular or lung injury, skin tenting over the site, and open fracture or concurrent glenoid fracture (as this leaves the upper extremity without bony attachment to the thorax). There is controversy regarding the degree of displacement which should mandate operative intervention, but data [20] supports the non-operative management of fractures with less than 2 cm displacement.

Distal Clavicle Fracture

Distal fractures are subdivided into categories (Table 2) based on the location and characteristics of the injury. Types 1, 3, and 4 may be able to be managed non-operatively. Management of type 2 fractures is controversial. Non-operative management has very high rates of non-union without operative intervention [15], but some evidence suggests this may not significantly impact patients' functional outcomes. In all cases non-operative management consists of sling immobilization with physical therapy for range of motion and strengthening once tenderness has resolved [1].

Proximal Clavicle Fracture

While quite rare, accounting for less than 3% of clavicle fractures, those involving the proximal third of the bone are significant for several points. First, due to the bony overlap and often minimal displacement, X-ray lacks sensitivity for proximal fractures, and if negative, CT should be considered [18]. Second, due to the much higher forces typically required to cause a proximal clavicle fracture, there is a very high (>80%) rate of clinically significant neck, head, or intrathoracic injury in traumatic fractures, mandating operative intervention in most cases. In patients who present with atraumatic (stress) fractures, management is with sling immobilization as in distal fractures.

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Table 2 Classification and management of distal clavicular fractures

Fracture category	Definition	Management
Type 1	Fracture lateral to coracoclavicular ligament Ligaments remain intact on both fragments preventing displacement	Non-operative
Type IIA	Fracture medial to coracoclavicular ligament Ligaments remain intact but only insert on distal fragment allowing superior displacement	Operative
Type IIB	Coracoclavicular ligament injury allowing displacement of medial fragment	Operative
Type III	Intra-articular fracture involving AC joint	Non-operative
Type IV	Physeal fracture in children Ligaments intact	Non-operative
Type V	Comminuted fracture	Operative

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Disorders of the Lower Extremity 116

Jeff Leggit, Ryan Mark, Chad Hulsopple, Patrick M. Carey, and Jason B. Alisangco

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The lower extremities provide the stable platform for locomotion and all movements while upright. They are subject to much higher force loads than the upper extremities. Walking has an impact force of 1.2–3 times a patient's body weight (BW), and running can increase the impact force anywhere from 7–10 times BW. Compounded over a lifetime, the lower extremities are subject to tremendous loads. Multiple intrinsic and extrinsic factors increase the risk for lower extremity injuries. These include but are not limited to musculoskeletal abnormalities (e.g., pes cavus), obesity, advancing age, chronic illness (e.g., diabetes, COPD), training errors, certain medication use, and previous trauma.

This chapter will discuss in detail those conditions most commonly seen and managed by the family physician in an ambulatory setting as well as those less common entities that have high morbidity if not properly recognized.

Hip Injuries

Hip Fracture

General Principles

General principles worldwide there are approximately 1.66 million hip fractures per year, with 95% occurring in adults age 60 or greater. Mortality rates associated with hip fracture approach 14% in the first 30 days following the fracture and 17–37% within the first year. Aging is associated with several impairments including osteoporosis, muscle weakness, imbalance, hearing loss, and presbyopia. These age-related factors combined with comorbid medical disorders and polypharmacy place seniors at high risk for falls and subsequent hip fractures. With the aging population, it is estimated there will be more than six million hip fractures per year by 2050 [1].

Diagnosis

Classically, patients will present with sudden onset of hip pain and inability to walk after a fall. However, it is important to remember those with minimal displacement or impaction fractures may be able to ambulate. Insufficiency fractures (normal stress to abnormal bone causing a fracture) may occur in the absence of overt trauma. Additional presenting complaints concerning for hip fracture include pain in the groin, thigh, buttock, or knee. Physical exam will show localized tenderness in the hip and groin with limited range of motion.

Initial assessment of the patient with a hip fracture should focus on a complete history and physical exam as there may be coexisting injuries (e.g., traumatic brain injury). Radiographic examination should include anterior/posterior (AP) pelvis and cross-table lateral hip views with careful avoidance of frog leg positioning due to risk of fracture displacement. Computed tomography (CT) scanning is useful when plain films are inconclusive. Any elderly or at-risk patient (i.e., chronic steroid use or known osteoporosis) with hip pain and a history of a fall requires a thorough radiographic assessment. The differential diagnosis includes dislocation, ligamentous sprain, muscle injury, and chondral or labral pathology. (Note that many of these conditions may coexist with any fracture.) See Table 1 for a list of differential diagnosis for hip-related pain.

Treatment

Immediate treatment of an isolated hip fracture (except avulsion fractures) consists primarily of providing adequate analgesia and urgent orthopedic surgery consultation. Most fractures should be repaired surgically within 48 h. However, nonoperative management is appropriate when surgical risk is too great or when life expectancy is limited.

The family physician may be asked to assist with pre- and perioperative management to include cardiac risk evaluation. The most current American Heart Association and American College of Cardiology guidelines should be consulted for the latest recommendations, but in general if there are no active cardiac conditions and the patient had been able to walk a flight of stairs, surgery can proceed [2].

Antithrombotic agents should be used for at least 10–14 days and up to 35 days postoperatively per the American Academy of Chest

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Table 1 Differential diagnosis of hip pain disorders of the lower extremity

Very common	Common	Infrequent	Referred
Osteoarthritis Tendinopathy[a] Muscle strains[a] Bursitis[b] Iliotibial band syndrome (proximal) Sacroiliac disorders	Synovitis (femoral acetabular) Inguinal hernia Labral tear Femoral acetabular impingement Nerve entrapment[c] Stress fracture Traction apophysitis[d] Acute fractures Chondral lesions Snapping hip [e] Tensor fascia lata syndrome Bony contusion (iliac crest) Coccyx injury	Hip dislocation and subluxation Sportsman's groin (sports hernia, athletic pubalgia) Pubic symphysis dysfunction (osteitis pubis) Osteonecrosis (avascular necrosis) Ligamentum teres rupture Inflammatory or crystalline arthropathy Slipped capital femoral epiphysis Legg-Calve-Perthes disease – Os acetabuli (extra ossification at superior surface of acetabulum) Malalignments	Lumbar/sacral disk/nerve pathology Septic arthritis Claudication, aorta/iliac insufficiency (Leriche's syndrome) Herpes zoster Pelvic/abdominal pathology Tumor Complex regional pain syndrome

[a]Gluteal, iliopsoas, adductor, quadriceps, hamstring, piriformis
[b]Greater trochanteric, iliopsoas, ischial
[c]Lateral femoral cutaneous (meralgia paresthetica), iliohypogastric, ilioinguinal, genitofemoral, femoral, saphenous, obturator
[d]Ischial tuberosity (origin of the hamstrings); anterior inferior iliac spin (origin of the rectus femoris); anterior superior iliac spine (the origin of the sartorius); pubic symphysis (origin of the adductor brevis and longus/gracilis)
[e]Internal due to iliopsoas or labral pathology and external due to iliotibial band

Physicians. While there is no consensus to the exact regiment or optimal duration, it is agreed up that antithrombotic prophylaxis with a combination of pharmacologic and mechanical device should be used. Aspirin is not recommended as a single pharmacologic agent for prophylaxis following surgery for hip fracture [3].

The family physician has a major role in primary and secondary fracture prevention which are very similar and include risk factor reduction through smoking cessation, moderation of alcohol use, osteoporosis management (prevention, detection, and treatment), and fall prevention (to include home assessment). Reducing polypharmacy and medication reconciliation should also be addressed. High-risk medications include sedatives, hypnotics, behavioral health medicines, antihypertensives, and anticoagulants. Although the best strategy for restoring mobility and function after a fracture has not been determined, a combination of weight-bearing exercise, proprioception/balance training, and muscle strengthening is advocated. Prophylaxis with bisphosphonates should be offered regardless of osteoporosis status to those patients with hip fractures receiving a prosthetic. The use of bisphosphonates has been shown to increase prosthetic survival [2]. Bisphosphonates should be administered along with appropriate doses of calcium and vitamin D unless contraindications exist. A recent review of cushioned hip protectors showed that they have little effect on hip fractures and compliance is poor at best [4].

Stress Fractures

General Principals

Lower extremity stress fractures account for 80–90% of all stress fractures and up to 20% of sports related injuries [5]. Table 2 lists intrinsic and extrinsic risk factors which must be addressed for prevention as well as recurrence avoidance. Around the hip, femoral neck stress fractures

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Table 2 Intrinsic and extrinsic risk factors for stress fractures and overuse injuries of the lower extremity

Intrinsic risk factors		Extrinsic risk factors	
Hormonal factors Leg length abnormality Foot abnormality	(E.g., estrogen deficiency) Functional∗ vs. true∗∗ Pes cavus/planus Rearfoot varus Hypermobile first ray Short first ray or long second ray	Training regimen∗	Volume Intensity Duration Inadequate recovery time New activity Poor technique
Hip	Excessive hip external rotation Femoral ante/retroversion		
Knee	Genu valgum/varum Patella alta Tibia vara/torsion		
↓ Muscle endurance ↓ Bone mass ↓ Lower body muscle mass		Medications	
		Improper nutritional habits	♀ athlete triad
		Running surface	Hard Soft Canted
Muscle imbalance Genetic factors Metabolic factors		Smoking	
		Environmental factors	Hot Cold Humid
		Improper equipment	Shoe∗∗
∗Functional leg length abnormality is measured by relative heights of iliac crests standing and or umbilicus to medial malleolus. Difference of ≥1 cm is considered significant and prompts evaluation for true leg length abnormality vs. functional due to pelvic obliquity. Treat with shoe inserts in shorter side or manipulation of obliquity ∗∗True leg length abnormality is measured from a fixed point to a fixed point – anterior superior iliac spine to medial malleolus. Difference of >1 cm is considered significant and should prompt evaluation (scanogram) and treatment (foot insert or surgical correction)		∗Stress fractures (as well as overuse conditions) are preceded by 4–12 weeks of an increase in physical demand without adequate recovery time interposed Recommendation is to only increase one parameter at time and not more than 10% a week ∗∗Minimalist vs. shock absorber or pronator vs. supinator (evidence-based recommendations cannot be made and sound training practices are more prudent than shoe type in preventing injuries) Loss of structural support from worn shoes (q 6 months or 500 miles)	

(FNS) are associated with high morbidity if not promptly diagnosed and appropriately managed. Female athletes and those unaccustomed to running or impact forces (e.g. basic military recruit) are the most common patient populations. Pain can be focal or diffuse and even radiate to the knee.

Diagnosis

There is a paucity of physical exam findings related to bone stress injury, and a high index of suspicion is required for proper identification. It would be prudent to have patients be non-weight-bearing while awaiting a definitive diagnosis. Definitive diagnosis requires radiographic confirmation. Plain radiography should be ordered but radiographic findings often lag or are very difficult to appreciate. Bone scans lack specificity and remain positive for months to years even after a patient has fully recovered and therefore are not recommended. Magnetic resonance imaging (MRI) is the modality of choice for diagnosis.

Consider bone mineral density testing if history of multiple low-risk stress fractures or a single high-risk stress fracture.

Treatment

Stress fractures can be segregated into low and high risk depending on their location and ability to heal. See Table 3 for a list of each type of fracture and treatment recommendations based on type. If confirmed, all patients with FNS should be referred for definitive management and immediately be placed on non-weight-

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Table 3 Low- and high-risk stress fractures of the lower extremity

Low risk	High risk
Generally occurs to cortical bone	*Generally occurs to cancellous (spongy) bone*
Femoral shaft	Femoral neck
Medial tibia	Patella
First to fourth metatarsal	Anterior tibial diaphysis
Treatment recommendations	Talus
Must off-load (can use crutches, cast, walking boot, or rigid shoe depending on site). Gradually resume weight-bearing as symptoms allow while restoring strength and flexibility	Tarsal navicular
Correct risk factors	Fifth metatarsal
	Treatment recommendations
	Refer to musculoskeletal specialist due to high morbidity
	Correct risk factors

bearing status of the involved lower extremity [6]. Treatment of FNS consists of internal fixation vs. strict non-weight-bearing. Stress fractures of the tension side, superior aspect of the femoral neck, should be considered urgent and referred to an orthopedic surgeon. Stress fractures of the compression side, inferior aspect of the femoral neck, may be treated with non-weight-bearing status dependent on the severity of the fracture. Treatment, in the primary care setting, should focus on the identification and modification of risk factors. The majority of low-risk stress fractures will heal with conservative management between 8 and 14 weeks. Management of high-risk stress fractures should include a strong consideration for referral.

Avulsion Fractures

The hip contains a number of apophyseal sites which are subject to injuries ranging from apophysitis to fractures (avulsions or stress). See Fig. 1 for hip and upper leg anatomy. Avulsion injuries are rare and are more commonly seen in the adolescent population secondary to muscle contraction against an open growth plate. Unless an avulsed fragment is displaced >2 cm, nonoperative management is recommended and consists of partial weight-bearing in conjunction with decreased activity for a 3–6 week period. This is followed by gradual resumption of activity as pain allows. Correction of any modifiable risk factors (Table 2) is required to prevent recurrence.

Hip Dislocation

General Principles

The focus of this section is simple dislocations of the femoral head outside of the acetabulum. Complex dislocations have an associated fracture, and after the dislocation is reduced, fracture management dictates therapy. Dislocations are not subtle injuries and require immediate referral to an orthopedic surgeon. The most common mechanism of injury is a high-energy motor vehicle accident which carries the risk of other major traumatic injuries. Other mechanisms include a fall from a height, automobile-pedestrian accidents, and athletic injuries [7]. Posterior dislocations are most common and present as a flexed, adducted, and internally rotated leg. Anterior dislocations are rare and more likely to occur during sporting events. These patients will present with the lower extremity in external rotation with slight flexion and abduction.

Diagnosis

Because of the high-energy mechanism of injury, a thorough clinical examination should be performed beginning with airway, breathing, and circulation following standard Advanced Trauma Life Support® protocols. Additionally it is important to assess for neurologic or vascular injury. An AP pelvis radiograph is usually adequate for the diagnosis of a hip dislocation. A posteriorly dislocated femoral head appears smaller than the contralateral side and will be outside of the acetabulum, while an anteriorly dislocated femoral head appears larger. A cross-

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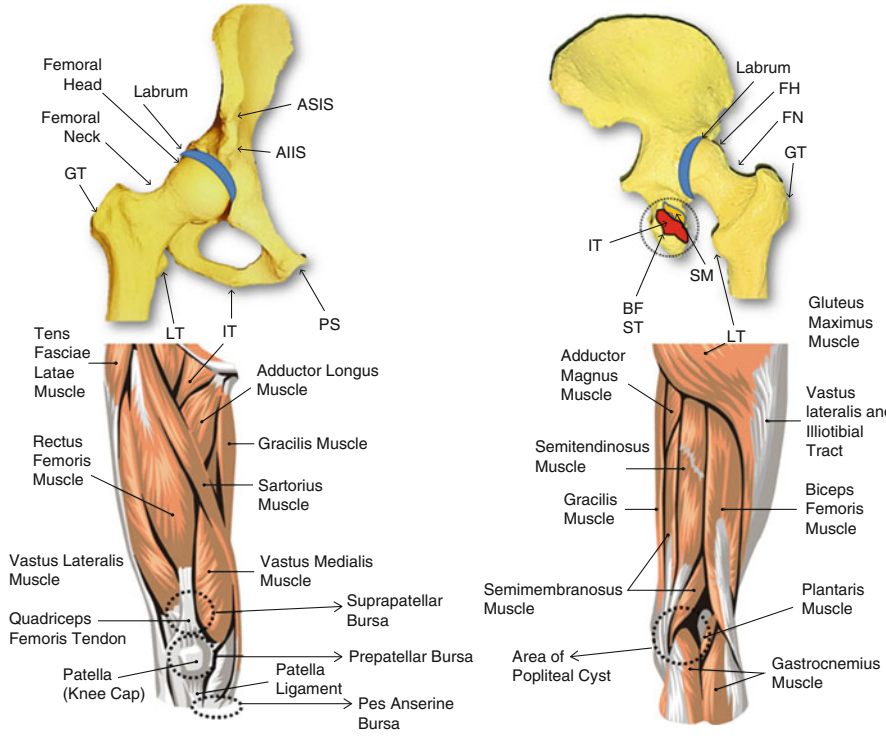


Fig. 1 Hip and upper leg anatomy. AIIS anterior inferior iliac spine (rectus femoris origin), ASIS anterior superior iliac spine (sartorius origin), PS pubic symphysis (adductor brevis/longus and gracilis origin), IT ischial tuberosity (hamstring origin (BF biceps femoris/ST semitendinosus/SM semimembranosus)), GT greater tuberosity (gluteus medius/minimus insertion), LT lesser tuberosity (iliopsoas insertion), FH femoral head, FN femoral neck (Muscle figures adapted and used by permission from fpnotebook.com)

table lateral film provides a second view of the relationship of the femoral head to the acetabulum. Unless there is suspicion of an occult femoral neck fracture, a CT is not needed prior to emergent reduction. The differential diagnosis is the same as for fractures but includes subluxations.

Treatment

Hip dislocation is a severe injury that requires prompt attention. Emergent reduction reduces the period of avascularity to the femoral head and should be accomplished as atraumatically as possible and ideally within 6 h. If neurovascular compromise is not present, a fracture should be ruled out prior to any attempts at reduction. If there is no associated fracture on postreduction films and proper joint alignment is achieved, the leg should be extended and externally rotated, and a knee immobilizer should be placed to prevent inadvertent flexion at the hip. All patients with hip dislocation must be referred to an orthopedic surgeon who will guide rehabilitation. Patients are at risk for avascular necrosis and subsequent osteoarthritis (OA). They should be encouraged to maintain an ideal body weight as well as core and hip strength to mitigate morbidity.

Femoroacetabular Impingement (FAI) Syndrome

General Principles

Femoroacetabular impingement (FAI) syndrome comprises a constellation of bony overgrowth conditions secondary to adaptation or malformation in and around the hip joint. There can be involvement of the acetabulum, the femoral head, or a combination of the two

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[8]. The impingement deformities include acetabular overgrowth or acetabular retroversion (abnormal position changing the way the femur articulates with the acetabulum) producing a pincer (pinching) lesion and femoral neck bony buildup producing a cam or "pistol-grip" deformity (abutting up against a normal acetabulum). However, the most common is a mixed type with features of both (see Fig. 2). The condition is most commonly seen in the athlete population, with an increased prevalence identified in the young, the female, and the Caucasian populations. Long-standing FAI may lead to acetabular labral injury, damage to the articular cartilage and osteoarthritis.

Diagnosis

Pain related to FAI is insidious in onset, and patients will commonly complain of groin pain but can also experience pain in the buttock, lateral or anterior thigh, and low back. There is often a reduced range of motion and/or pain in internal rotation and flexion. Patients may state that they need to frequently change positions while sitting to alleviate pain. Diagnosis is usually delayed because of the vague nature of the complaints and the lagging radiographic changes.

Young athletic males more commonly are affected by cam lesions. Cam-type deformities can lead to chondral damage, labral tears, and

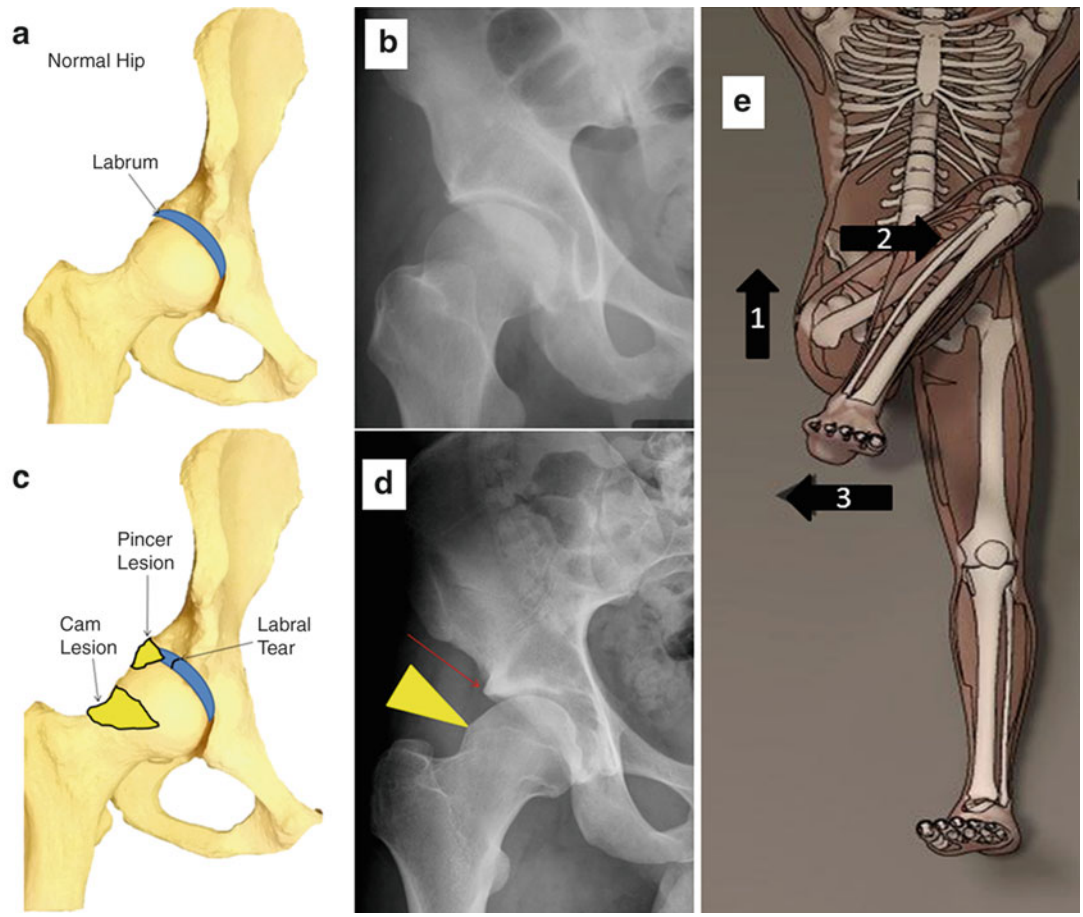


Fig. 2 Femoroacetabular impingement and FADIR test. (**a**) Normal hip anatomic model. (**b**) Normal hip AP radiography. (**c**) Hip anatomic model with cam and pincer lesion and labral tear. (**d**) AP radiography with cam lesion (*yellow arrowhead*) and pincer lesion (*red arrowhead*). (**e**) FADIR test: flexion (*arrow #1*), adduction (*arrow #2*), internally rotate (*arrow #3*) (FADIR image adapted with permission from fpnotebook.com)

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early OA due to abnormal abutment forces on the acetabular labrum. Middle-aged active women are more likely to present with pincer lesions. Their pain results from the over-coverage of the femoral head or acetabular retroversion which appears on plain films as an anterior osteophyte from the superior lateral acetabulum. As mentioned earlier, a mixed cam and pincer deformity is the most common presentation (see Fig. 2). Patients with concomitant labral tears may present with mechanical symptoms of clicking and catching.

Evaluation should include a complete lumbar and lower extremity physical exam specifically assessing for obvious anatomic malalignments (leg length discrepancy, lower limb valgus/varus position, pes cavus/planus), decreased range of motion, and hip weakness. The tests most consistent with FAI include a painful supine impingement test or FADIR test (hip **f**lexion to 90°, **ad**duction, and **i**nternal **r**otation; see Fig. 2) along with a painful resisted straight leg raise. (The pattern of inspection, palpation, range of motion, motor strength, and special tests constitutes the essential elements of all musculoskeletal physical examinations and will be repeated throughout the chapter.)

If FAI is suspected, radiographs should be obtained, including at minimum a standing pelvis AP and a lateral view. Additional images such as frog leg and possibly a Dunn view (AP pelvis with the hip at 20° abduction and either 45° or 90° flexion) may further help to evaluate femoral head/neck morphology. Plain MRI has little role in FAI evaluation; however MR arthrogram can serve two purposes: first the contrast material can help identify chondral and labral lesions which have important treatment implications, and secondly the intra-articular anesthesia injected for the procedure can serve a diagnostic role in identifying the hip joint as the primary source of pain. CT is utilized for defining the three-dimensional bony abnormalities but is reserved for the treating surgeon for surgical planning. The differential diagnosis includes tendinopathies and chondral or labral pathologies (see Table 1).

Treatment

Recent evidence suggests that conservative management with a physical therapy-based treatment plan results in improvement of functional status and pain reduction for patients with FAI. Additional pain control, either orally or via intra-articular injections, may be used to augment physical therapy. Exercises directed at strengthening the hip abductors, pelvic stabilizers, and abdominal core muscles as well as correcting any contractures of the hamstrings, iliopsoas, quadriceps, or iliotibial band are recommended regardless whether nonsurgical or surgical options are pursued [9]. (This reference contains examples of home exercise handouts for a variety of conditions and is suggested for prescribing home rehabilitation therapy.) Arthroscopic surgery is the definitive treatment for FAI. The mainstay of surgery is the removal of any mechanical obstructions. One of the benefits of surgical intervention is the ability to correct underlying soft tissue injury, such as labral tears, as well as removal of the mechanical obstruction.

Acetabular Labral Tear (ALT)

General Principles

The acetabular labrum is a fibrocartilaginous structure lining the acetabular socket (see Fig. 1). It is vascularized only in the outer third and pain-sensing nerve fibers parallel the blood supply. The lack of robust blood supply explains why the labrum has a poor potential to heal; a similar concept will be discussed in the knee meniscus. The hip labrum serves to aid in stability and force disbursement. Acetabular labral tear (ALT) is both common and frequently asymptomatic. A cadaveric study found that 93–96% of hips demonstrated a tear of the acetabular labrum [10].

An ALT can result from an acute injury or abnormal force pattern stemming from femoral acetabular incongruities (e.g., FAI). Symptomatic ALTs can present suddenly after a traumatic event, but much more often present with an insidious onset of groin, lateral, anterior, and posterior hip pain. Acetabular labral tears are undiagnosed for an average of 2 years owing to their vague pain

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pattern and lack of distinct physical exam techniques.

Diagnosis

ALT often presents as anterior groin pain that worsens with loading of the joint. This can include prolonged periods of standing, sitting, or walking. Sharp pain often accompanied by mechanical symptoms such as clicking or catching is frequently described. When patients are asked to identify the painful area, they will cup the hip with their forefinger and thumb ("C" sign). As with all disorders of the hip, physical examination must include a visual inspection for lower extremity malalignments, points of tenderness, range of motion, motor strength, and special tests. The FADIR test, described earlier (see Fig. 2), has the most substantiating evidence for intra-articular pathology and therefore can guide one in the direction of diagnosis. Other tests have been described but lack quality supporting evidence.

Imaging of the painful hip should begin with radiographs, including at a minimum a weight-bearing AP (whenever possible radiographs should be weight-bearing for any lower extremity conditions). In patients with a suspected ALT, radiographs should be analyzed for abnormal morphology of the acetabulum and femoral head, including anatomy predisposing to FAI (see Fig. 2). MRI with contrast (MR arthrogram) is the imaging modality of choice and can demonstrate a displaced labral flap or irregular labral morphology. A paralabral cyst is a small collection of fluid communicating with the labrum or the cartilage-labral junction, when noted is pathognomonic of a labral tear. Intra-articular anesthetic hip injection can also be helpful in the diagnosis of intra-articular pathology. This injection can be done at the time of MR arthrogram or separately via ultrasound-guided injection or fluoroscopy. Just as in FAI, if intra-articular anesthesia alleviates the pain, the hip joint can be assumed to be the source of the pain. Arthroscopy remains the gold standard for the diagnosis of ALT. No single patient history or clinical examination findings are "stand alone" in their ability to diagnose ALT. An emphasis on the summative patient history, clinical examination findings, imaging modalities, and intra-articular anesthetic injection response is needed to diagnose a symptomatic ALT. The differential diagnosis (Table 1) includes tendinopathies, FAI, and chondral lesions.

Treatment

A trial of conservative management, including relative rest and oral analgesic medications, combined with a focused physical therapy protocol is recommended. Therapy should focus on strengthening the hip, pelvis, and abdominal core musculature in addition to addressing flexibility deficits (see Ref. [9] for home exercises). A trial of intra-articular injection with steroid under imaging guidance can be offered; however one must keep in mind that repeated injections with corticosteroid may damage chondral surfaces and are not recommended. Additional intra-articular injectable therapies are available but lack high-quality supporting evidence at this time. When conservative measures do not control the patient's symptoms or when functional limitations remain unsatisfactory, a referral for orthopedic surgery is appropriate.

Greater Trochanteric Pain Syndrome (GTPS) or Trochanteric Bursitis

General Principles

GTPS is a common overuse syndrome involving one or a combination of greater trochanteric bursae, iliotibial (IT) band and gluteus medius and gluteus minimus muscle and/or tendon (see Fig. 1). The primary action of these muscles is hip abduction. There may be up to 3–4 bursae in this region. A bursa is a small synovial-lined structure that helps tissues glide over one another, as when a tendon slides over another tendon or bone. Greater trochanteric bursitis previously was theorized to be caused by repetitive trauma from friction which leads to bursitis or inflammation in the region. More recent evidence from imaging studies have shown most patients with the diagnosis of bursitis have little or no bursal inflammation and more commonly tendinopathy (disease of the tendon) of the hip abductors [11].

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Diagnosis

GTPS is characterized by pain and tenderness over the bony prominence of the posterior lateral thigh. Pain may start after a specific trauma or have an insidious onset. Patients may complain of pain in the lower buttocks and the lateral aspect of the thigh when lying on the hip, walking, running, climbing stairs, or when standing on the affected leg. Pain may radiate down the lateral aspect of the leg along the pathway of the IT band.

Evaluation of a patient with GTPS should include a full history and physical exam of the back, pelvis, and lower extremities. The presence of weakness, contractures, asymmetry, and pain in other areas such as the lower back, groin, knees, ankles, and feet can contribute to the syndrome. The family physician should assess for malalignments of the lower extremity, gluteus medius weakness, and tightness of the IT band. Pain on direct palpation is the most sensitive and specific finding. Often the culprit is a gluteal insertional tendinopathy. Active abduction, engaging of the gluteus medius/minimus muscles, and passive adduction, stretching of the involved muscle, are painful and can exacerbate this lateral hip pain. Reproduction of index pain with a 30 s single-leg stance test is highly suggestive of a gluteal tendinopathy and is also used to detect a positive Trendelenburg sign. A positive or abnormal Trendelenburg sign is when the patient demonstrates an abnormal lateral pelvic tilt while assuming a single-legged stance on the affected side in an effort to overcome hip weakness on the painful limb (see Fig. 3).

GTPS is a clinical diagnosis. Imaging is pursued when the diagnosis remains unclear or the patient is not responding to appropriate therapy. Plain film radiography may show trochanteric exostoses or osteophytes suggesting calcific tendinopathy or bursopathy in long-standing cases of GTPS. MRI may show degenerative changes to the gluteus medius and minimus tendons. Ultrasonography has emerged as an effective imaging modality for identification of normal vs. pathologic appearance of the structures involved. An added benefit of ultrasonography is

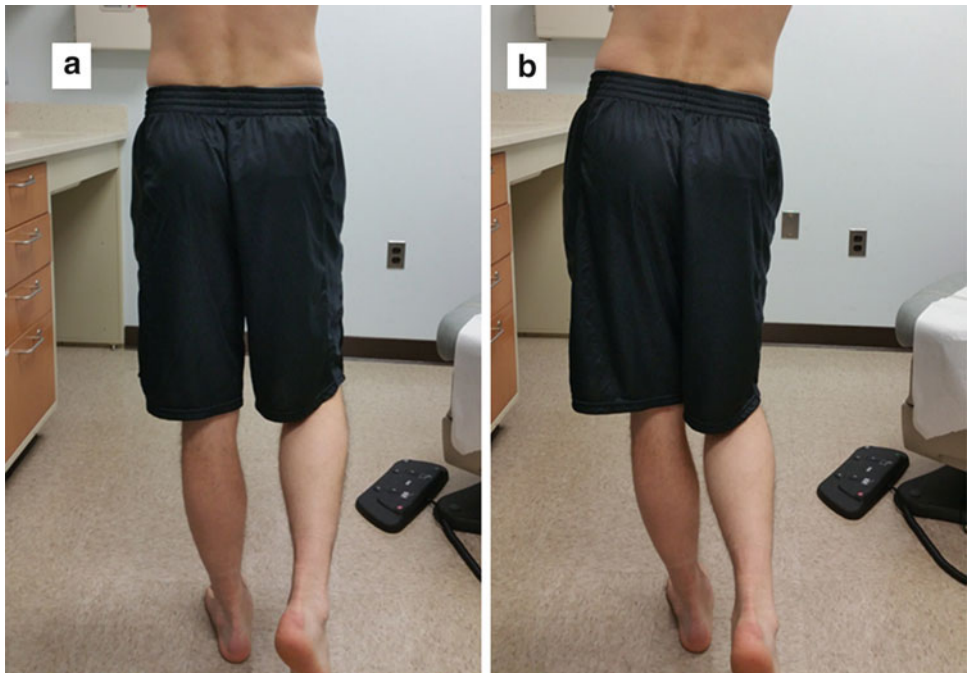


Fig. 3 Trendelenburg sign – patient stands on affected leg and lifts the unaffected leg from floor. (**a**) Normal response – ability to maintain pelvis in neutral position. (**b**) A positive or abnormal sign manifested by inability to maintain neutral posture when standing on the affected leg (non-weight-bearing hip will drop below the weight-bearing hip)

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the ability to perform a dynamic exam for reproduction of patient reported symptoms.

Treatment

GTPS typically responds to conservative measures, such as activity modification, physical therapy (PT) aimed at strengthening the hip (specifically the gluteal muscles – see Ref. [9] for home exercises), and correction of any contractures. Weight loss is appropriate if indicated and can dramatically improve pain. Interventions to relieve pain are required if pain precludes daily activities, sleep, and/or participation in rehabilitative exercises. (These principals hold true for all lower extremity conditions.) Ice massage may suffice, but the short-term use of acetaminophen or NSAIDs may be warranted. If these modalities do not provide adequate symptomatic relief, corticosteroid injection into the associated bursa can be entertained. Long-term studies have shown steroid injections alone to be inferior to PT, and they should not be used as sole treatment. (This concept also holds true for most overuse conditions.) While studies on the effectiveness of regenerative (platelet-rich plasma – PRP) and proliferative (prolotherapy) injection therapies have lacked consistency, their use in treating various tendinopathies is growing in popularity and use [12]. They should be considered when pain and dysfunction persist despite appropriate rehabilitation. These treatments should be performed in conjunction with strengthening and stretching. Extracorporeal shock wave therapy has shown potential benefit and may be an option. Surgical treatment is reserved for patients who have completed a minimum of 6–12 months of conservative management but remain symptomatic.

Quadriceps and Hamstring Injuries

General Principles

Injuries to the anterior and posterior thigh are extremely common and can be a source of long-term morbidity especially for the high-level athlete. Thigh injuries can account for up to 13.5% of all sports injuries [13]. The quadriceps muscles, comprised of the rectus femoris and vastus lateralis/intermedius/medialis, are the primary knee extensors. The hamstring muscles are the primary knee flexors and consist of the bicep femoris, semimembranosus, and semitendinosus. The quadriceps have different origins but a common insertion point (superior pole of the patella), while the hamstrings are the opposite (see Fig. 1). Both muscle groups are prone to acute injuries (avulsions, tendon tears/strains, muscle contusions/tears) and chronic tendinopathies. It is important to remember that the hamstring muscles (with the exception of the short head of the biceps femoris) and the rectus femoris of the quadriceps are biarticular muscles (span two joints) and thus are more prone to injury.

Diagnosis

When attempting to identify the etiology of thigh pain, there are two important factors to consider, the location and the mechanism of injury. Contusions will be focal and the result of a direct blow or fall, while tears/strains usually occur with bursts of speed/kicking/stretching, both can have significant bruising and swelling. A chronic poorly localized pain pattern should raise suspicion of a stress fracture or referred pain (see Table 1). Pain at the bony origin raises the suspicion of an avulsion injury. While strains more commonly occur at the myotendinous junction.

Range of motion should be gently assessed. Strength testing can be challenging in the acute setting as loss of strength can be secondary to pain as well as injury. The degree of pain and weakness is a predictor of injury severity and thus recovery time. Special tests for referred pain (i.e., radiculopathy or sacroiliac dysfunction) are reserved for those cases that are not straightforward or are not responding to appropriate treatment. Imaging with ultrasound or MRI is largely reserved for refractory cases or when the diagnosis is in question, with the exception of suspected stress fracture as discussed earlier in this chapter.

Treatment

The first 24 h is the most critical time for quadriceps contusions. The goal is to maintain maximal flexion and minimize bleeding. This is accomplished by having the patient flex the knee as

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much as possible and maintaining this position for 24 h with the use of an elastic bandage and the almost continuous use of ice over the tender area. Soft tissue therapy (i.e., massages) is contraindicated acutely for risk of rebleeding. After the first 24 h, patients can begin a gentle stretching program to tolerance and progress as symptoms dictate. Local control of pain can be accomplished with oral (acetaminophen, NSAIDs) and topical (lidocaine, NSAIDS) analgesics or ice. NSAID use has not been found to decrease the incidence of complications, specifically myositis ossificans. Once full range of motion is achieved, then strengthening should commence (see Ref. [9] for home exercises). Symptom-based progression is discussed in greater detail under the treatment section of calf injuries. Symptom-based progression serves as a template for rehabilitation principles for quadriceps and hamstring injuries as well. Treatment of quadriceps strains is largely the same as to treatment of quadriceps contusions, keeping in mind that patients may take a longer amount of time for full recovery from strain as compared to contusion.

Large contusions can lead to the development of myositis ossificans (MO), a calcification of a hematoma. MO present as a hardening mass. Currently, there is no adequate therapy to treat once present. If there is no history of trauma to explain the calcified mass, a workup for a tumor should be undertaken.

Hamstring tears can be divided into types 1 and 2. Type 1 occurs at the proximal portion of the long head of the bicep femoris and is the result of an explosive burst, i.e., sprinting. Type 2 occurs at the ischial tuberosity at the origin of the semimembranosus and is related to excessive stretch (i.e., full knee extension combined with hip flexion) [14]. (see Fig. 1). The rehabilitation is similar, though type 1 injuries have a tendency to recover quicker compared with type 2 injuries, and patients should be advised as such. Rehabilitation begins with restoring full range of motion followed by a focus on regaining strength and culminates in activity- or sport-specific drills (see Ref. [9] for home exercises). The use of a thigh compression sleeve is recommended in the acute, chronic, and rehabilitative setting. These injuries have a high rate of recurrence, with prior hamstring injury being identified as a leading risk factor for future injury. Because of this the high-level athlete may be best served with a referral to a specialist for rehabilitation recommendations. Chronic hamstring and quadriceps tendinopathies are treated similar to GTPS and are also discussed in ▶ Chap. 55, "Athletic Injuries." They require addressing risk factors, biomechanical assessment, and strengthening of the involved muscle groups as well as the core muscles (see Table 2).

Knee Injuries

Meniscal Injuries

General Principles

The medial and lateral menisci are semicircular fibrocartilage structures with perfect congruity between the femur and tibia (see Fig. 4). This perfect congruity allows the menisci to dissipate force and provide joint stability as well as lubrication. Similar to the acetabular labrum, the adult menisci are only vascularized on the periphery, which leads to the concept of red and white zones (red zone with blood supply and white zone without blood supply). In general, red zone injuries have the potential to heal, while white zone injuries cannot heal. This is an important concept in treatment recommendations. Pain fibers parallel the vascularity and thus are located around the periphery as well. Loss of function leads to abnormal joint forces and accelerates cartilage damage and ultimately osteoarthritis.

Meniscus tears are categorized by type and location. Horizontal, radial, vertical (which includes bucket-handle tears), root tears, ramp lesions, and complex (which are a combination of the previous types) are frequently described. Horizontal and complex tears are most common and typically exist on the osteoarthritis spectrum. Radial and vertical tears are common in acute injuries, whereas root tears and ramp lesions are typically higher-energy injuries associated with ACL tears. In a study of patients aged 50–90 years, the prevalence of meniscus tear

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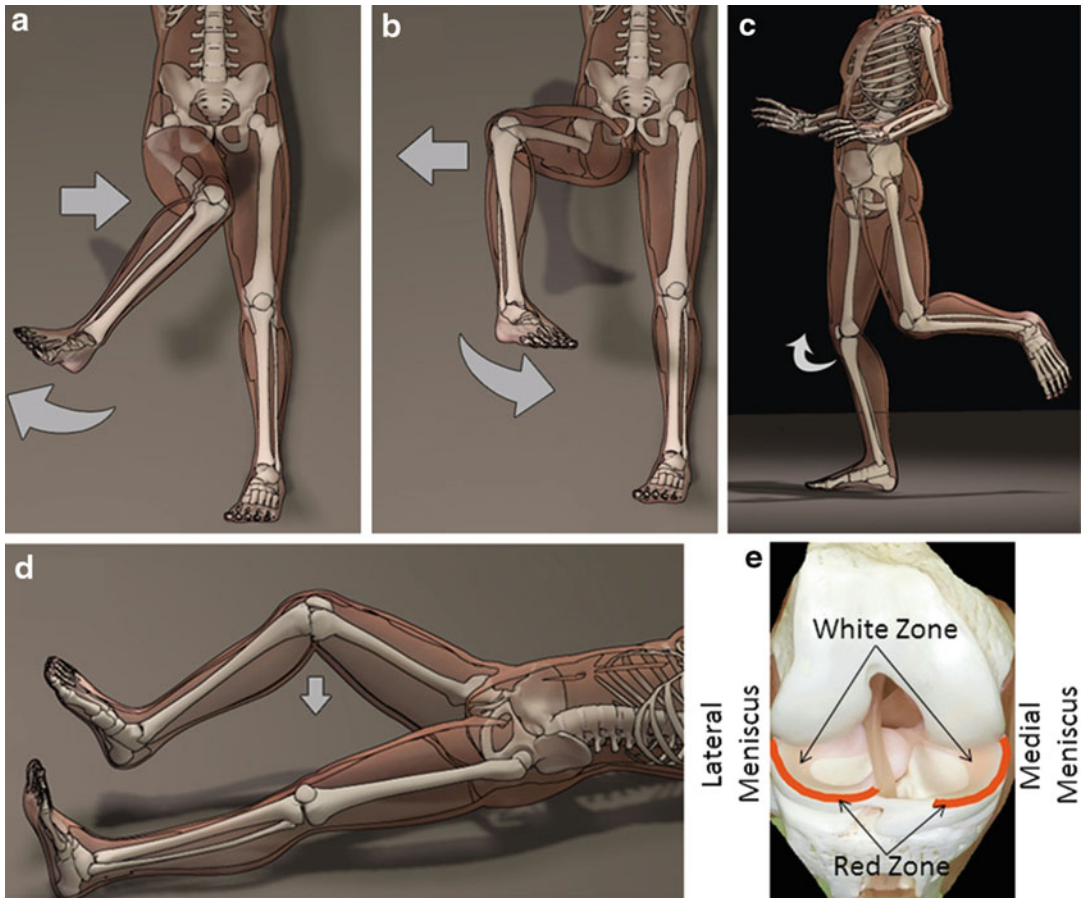


Fig. 4 Meniscal signs and anatomy. (**a**) McMurray test for medial meniscus – with fingers on medial and lateral joint line, flex the hip and knee maximally. Apply a valgus force (in direction of *straight arrow*) to the knee while externally rotating the foot (in direction of *curved arrow*) and passively extending the knee. A positive test is pain (with or without an associated click/snap) located on a respective joint line during movement (sensitivity ~65%; specificity ~65%). (**b**) McMurray test for lateral meniscus – with fingers on medial and lateral joint line, flex the hip and knee maximally. Apply a varus stress (in direction of *straight arrow*) during internal rotation of the foot (in direction of *curved arrow*) and passive extension of the knee. A positive test is pain (with or without an associated click/snap) located on a respective joint line during movement (sensitivity ~65%; specificity ~65%). (**c**) Thessaly test – hold patient's outstretched hands while he or she stands flat-footed on the floor, internally and externally rotating three times with the knee flexed 20°. A positive test is pain in respective joint compartment with movement (sensitivity ~85%; specificity ~90%). (**d**) Bounce home test – flex knee to 45 degrees and allow knee to fully passively extend (direction of *arrow*). A positive test is pain with passive extension (sensitivity ~45%; specificity ~75%). (**e**) Anatomic model of lateral and medical meniscus of right knee showing *red zone* (vascularized) and *white zone* (nonvascularized) (Figures **a**, **b**, **c**, **d** adapted with permission from fpnotebook.com)

was 31% [15]. Meniscal tear treatment has traditionally been with an arthroscopic partial meniscectomy (APM). While APM use has decreased over the last 15 years, it is still the most common orthopedic surgical procedure in the United States with 700,000 arthroscopic partial meniscectomies every year [16]. Recently the utility of this traditional practice has been called into question.

Diagnosis

Acute meniscal injuries present after a traumatic event. This can be a sudden noncontact twisting event (the most common mechanism) or through

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contact as in a football tackle. The presence of an acute effusion varies; an effusion generally denotes an injury to the vascularized red zone. Pain is the predominant feature. Other important historical elements are catching or locking, defined as a mechanical symptom of "something" inside the joint not allowing full pain-free range of motion. Physical examination findings can include a variable amount of intra-articular swelling (it is important to differentiate between soft tissue and intra-articular swelling), pain to palpation along the relevant joint line (anterior and posterior medial, anterior and posterior lateral), and pain with one or more of the meniscal tests (see Fig. 4). A thorough assessment for other ligamentous injuries (cruciate, collateral, patellar) is required as their injury has an impact on treatment recommendations.

Plain films consisting of an AP, lateral, and patellar view should generally be ordered if one is considering an acute meniscal tear in order to rule out a fracture, but other than showing an effusion, they are not diagnostic. Despite being able to adequately diagnose an isolated meniscal injury with history and physical exam in >90% of patients, an MRI is almost always ordered to confirm an acute meniscal tear. In addition to confirming the clinical suspicion, MRI is invaluable at detecting concomitant ligamentous injury and the presence of osteoarthritis or cartilage damage which have treatment recommendation implications. Unfortunately the MRI sensitivity of ramp lesions is only 48% [16].

Chronic (usually degenerative) injuries present with pain along the relevant joint line, intermittent swelling, and possible mechanical symptoms of locking and catching but lack the acute history of a traumatic event (although a careful history may reveal an antecedent event years previous that may have initially damaged the meniscus). Physical examination is similar as in the evaluation for acute injuries (see Fig. 4). The decision to image depends on the patient's symptoms and treatment preferences. A weight-bearing AP and lateral radiograph should be ordered as well as a patellar view (sunrise or merchant) to evaluate the presence and degree of OA which may affect treatment options. If the patient complains of true locking (a mechanical block to range of motion), then an MRI is warranted to confirm the diagnosis. Caution must be taken in interpreting meniscal tears on MRI though as they are present in approximately 20% of people without knee symptoms <40 years of age and up to 70% >65 years of age [17]. The differential diagnosis includes OA, chondral lesions, and patellofemoral pain syndrome (see Table 4).

Treatment

In general, patients under 40 and those without significant OA or cartilage damage are ideal candidates for meniscal repair. Acute meniscal tears warrant referral and should be repaired within 8 weeks of the injury. In chronic, degenerative tears, unless the patient has true mechanical symptoms (locking or catching), a discussion of treatment outcomes and joint decision-making is warranted. Since repair is generally not possible and once meniscal tissue is removed its function is lost permanently, symptom management becomes the treatment goals. Several randomized clinical trials have showed no significant differences in terms of knee pain relief, improved knee function, or patient satisfaction between APM and lower extremity strengthening exercises over 2–5 years of follow-up [18].

Baker's Cyst (Popliteal Cyst)

General Principles

Named after Dr. William Baker who first described the condition in 1877, a Baker's cyst is more properly termed a popliteal cyst. It is a fluid-filled mass generally resulting from the distention of a preexisting bursa in the popliteal fossa, most commonly the medial gastrocnemius-semimembranosus bursa (see Fig. 1). Unlike other bursa, this one is connected via a valvular opening in the joint capsule posterior to the medial femoral condyle and is present in up to 40–54% of healthy adult knee [19].

Diagnosis

Patients generally complain of fullness behind the knee. A mass can usually be seen and

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Table 4 Differential diagnosis of knee and calf disorders of the lower extremity

Very common	Common	Infrequent	Referred
Knee			
• Ligamentous injury (ACL, PCL, MCL, LCL) • Patellofemoral syndrome • Bursitis [a] • Patellar tendinopathy • Osteoarthritis • Chondral lesions • Iliotibial band syndrome (distal) • Meniscal injury	• Osteochondrosis (Sinding-Larsen-Johansson and Osgood-Schlatter) • Less common tendinopathy (quadriceps, proximal hamstring, popliteus) • Patellar instability (can be all directions) • Popliteal cyst	• Plica syndrome • Fat-pad syndrome (Hoffa syndrome) • Osteochondritis dissecans • Crystal-induced arthropathy • Stress fracture • Nerve entrapments (common peroneal, saphenous)	• Pigmented villonodular synovitis • Popliteal artery entrapment syndrome • Fabella syndrome
Calf			
• Gastrocnemius [b] • Stress fracture • Medial tibial stress syndrome [c] • Achilles tendinopathy	• Soleus [b] • Plantaris [b] • Fracture • Anterior tibial stress syndrome [d]	• Compartment syndrome (exertional and acute) • Nerve entrapment [e] • Achilles tendon rupture	• Infection • Tumor • Deep vein thrombosis
Differential diagnosis for acute hemarthrosis			
• Ligamentous injury • Meniscal injury • Patella injury • Extensor mechanism injury • Osteochondral injury • Fracture • Avulsion			

[a]Suprapatellar, prepatellar, deep infrapatellar, gastrocnemius, semimembranosus, sartorius, pes anserine, MCL bursa, distal iliotibial band, fibular collateral ligament, popliteus tendon
[b]Includes muscle strain/tears and tendinopathies
[c]Pain along posterior medial aspect of tibia believe to be periostitis of posterior tibial muscle, flexor digitorium longus and/or the soleus attachment on tibia
[d]Pain along the anterior aspect of tibia believe to be periostitis of anterior tibial muscle attachment on tibia
[e]Peroneal, sural, tibial

palpated in the prone patient with the knee fully extended. With knee flexion to around 45°, the cyst usually disappears or decreases in size. Confirmation can be obtained via ultrasound or MRI and should be performed if any doubt exists about the masses' etiology. A ruptured popliteal cyst can present with acute pain and signs of inflammation. An evaluation for a deep vein thrombosis (DVT) should be considered in this setting. The differential diagnosis includes tumors both benign and malignant as well as meniscal cysts and DVTs (see Table 4). Although popliteal cysts are most commonly found between the medial head of the gastrocnemius and semimembranosus, they have been reported in other areas. If a posterolateral cyst is discovered, further evaluation should be performed to rule out a meniscal cyst or soft tissue tumor as lateral presentation of popliteal cysts is unusual.

Treatment

Management is not dictated by the cyst but rather by the pathology that causes the cyst. OA with or without concomitant meniscal injury is usually the underlying cause in the majority of patients.

In those patients having mechanical symptoms due to a large cyst, ultrasound-guided aspiration can provide temporary relief, but the cyst will invariably return if the underlying pathology is not remedied.

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Knee Bursitis

General Principles

There are multiple bursas around the knee that can become symptomatic (see Fig. 1 and Table 4). Irritation of any of these bursas can cause knee pain. Definitive treatment lies in treating the underlying cause of the bursa irritation and not the irritation itself (see discussion on victims and culprits under GTPS). Local control of pain can be accomplished with oral (acetaminophen, NSAIDs) and topical (lidocaine, NSAIDs) analgesics or ice massages. Injections can be performed with steroids or other agents such as dextrose or platelet-rich plasma. Due to the great variability in bursa location, ultrasound-guided injections are recommended. It must be emphasized though that these are temporary measures and the underlying cause must be elucidated and corrected. Pes anserine bursitis will be discussed as it is prototypical and extremely common. Prepatellar bursitis will be mentioned as it has some unique features that must be taken into account.

Pes Anserine Bursitis

The diagnosis is easily made by tenderness at the pes anserine area and an appropriate history. The pes anserine bursa is generally located on the proximal medial portion of the tibia just superficial to the distal tibial insertion of the superficial medial collateral ligament (MCL) of the knee (see Fig. 1). This is the site for the common insertion point for the conjoined tendons of the sartorius, gracilis, and semitendinosus muscles. There is great individual variability in its exact location with most bursas lying between the three conjoined tendons and the tibia, less frequently between the MCL and the tendons, or between the tendons themselves. Because of the close approximation to the distal portion of the MCL, any history of a twisting injury or contact preceding the pain would warrant valgus loading of the knee in 0° and 30° to ensure the MCL is not sprained. In addition, medial meniscal tears can sometimes be confused or coexist with pes anserine bursitis (see Table 4). Treatment of pes anserine bursitis pain should include the local therapies mentioned in the "General Principles" section of knee bursitis and most importantly a search for and correction of the contributing factors:

- OA of the knee – as many as 75% of patients with OA have symptoms of pes anserine bursitis; knee and hip strengthening are the mainstays for OA treatment.
- Obesity – even a modest weight loss of ~5% may alleviate the pain.
- Valgus knee deformity, alone or in combination with collateral instability – bracing may be beneficial.
- Pes planus (i.e., flat foot) – consider foot orthoses.
- Diabetes mellitus (DM) – common comorbidity in a variety of bursitis. It is unclear if it is the obesity that accompanies DM or if it is the DM itself which causes the bursitis and it is also unclear if good glycemic control will minimize musculoskeletal complaints.
- Medial meniscal tear – loss of stability increases the forces over the pes anserine; see discussion on meniscal injuries for treatment recommendations.
- Saphenous nerve injury (from surgery, trauma, or mass effect) – needs a high index of suspicion for diagnosis and then must treat the cause.

Prepatellar Bursitis

Special note should be made concerning prepatellar bursitis, as an infectious etiology can be the cause. The following in declining order can be responsible for prepatellar bursitis [20]:

- Direct trauma (e.g., a fall on the patella or direct blow to the knee)
- Recurrent minor injuries associated with overuse (e.g., repeated kneeling)
- Septic or pyogenic process
- Crystal deposition (e.g., gout, pseudogout)

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If there is any concern for an infection (erythema, warmth, fluctuance), then at a minimum, an aspiration is required to analyze fluid content (white blood cells, protein, lactate, glucose, crystals, Gram stain, culture). Ultrasound greatly facilitates both confirmation of an enlarged bursa sac and is invaluable if an aspiration is considered. Fortunately, even if the bursa is infected, conservative treatment is warranted with aspiration of as much material as possible, and oral antibiotics that are narrowed once laboratory results are known (always consider methicillin-resistant *Staphylococcus aureus* and local antibiotic resistance patterns). Incision and drainage or bursectomy is reserved for patients with severe, refractory, or chronic/recurrent disease.

Fractures and Dislocations of the Knee

General Principles

Acute fractures of the knee are the result of trauma and are associated with an acute hemarthrosis. The differential diagnosis for an acute traumatic hemarthrosis in order of precedent is ligamentous injury (ACL being #1), peripheral meniscal injury, or a fracture (see Table 4). Quadriceps and patellar tendon tears are extra-articular structures but are associated with a large amount of soft tissue swelling. Their diagnoses are generally not difficult to make. Patients are unable to extend the knee and, because of their immediate loss of function, almost always present to the emergency room.

An acute fracture will present with focal tenderness over the involved bony area. Range of motion is usually limited by pain and unless there is a concomitant ligamentous/meniscal injury, special tests for the knee are normal. Plain radiography, at a minimum AP and lateral, is usually adequate to confirm the diagnosis, but if negative and clinical suspicion is high, an MRI would be warranted. Although CT is the imaging modality of choice for bony abnormalities, MRI will be able to diagnose the fracture as well as any other soft tissue abnormality that might be missed on CT. All fractures of the knee, which invariably are intra-articular, should be managed in conjunction with an orthopedist or a sports medicine physician in a timely fashion. (i.e., 48 h) In the interim depending on the degree of swelling, a compression wrap or hinged knee brace can be applied. Knee immobilizers are particularly painful and uncomfortable for patients and should never be left on for an extended period of time. If an in-person consultation cannot be achieved in an adequate timeframe, a telephone consultation to a specialist for treatment recommendations is warranted. Adequate pain control can generally be achieved with acetaminophen and/or NSAIDs.

Osteochondral defects and stress fractures can present more subtly and subacutely; therefore, a high index of suspicion is required. Osteochondral defects are focal areas of articular injury with damage to both the cartilage and the adjacent subchondral bone. Trauma is the leading cause of a focal osteochondral defect in a previously normal bone in the skeletally mature. The term osteochondral defect encompasses the entity known as osteochondritis dissecans (OCD). The acronym OCD is sometimes applied both to osteochondral defects and osteochondritis dissecans but technically should be reserved for the latter and will be the case in this chapter. The cause of OCD remains unknown but may include one or all of the following factors: genetic predisposition, defective skeletal development, vascular insult, and trauma. OCD usually begins in adolescents although its sequelae, premature OA may not become apparent until adulthood. Knee OCD frequency is reported to be 20/100,000 in 10–20-year-olds. Symptoms of any osteochondral defect include activity-related pain, catching or locking of the affected joint, and/or a transient effusion. OCD is often misdiagnosed as patellofemoral syndrome. Plain radiography includes AP view, lateral view, sunrise or merchant view, and a notched view, but an MRI is often required for diagnosis and is essential for staging. Adult osteochondral defects may present as an acute fracture or insidious as in an OCD.

When discovered, osteochondral defects should be at a minimum co-managed with an orthopedist or a sports medicine provider. Prognosis and treatment is dependent primarily on the stability of the lesion and the age of the patient.

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Adolescents with stable lesions can heal, but the skeletally mature are very unlikely to heal on their own [21].

Stress fractures of the knee are not common and require a high index of suspicion. Plain radiography can be suggestive, but generally an MRI is needed to confirm diagnosis. Management involves decreasing force loads and correcting any mitigating factors (see previous discussion on stress fractures).

Patella dislocations occur almost always laterally with the medial patellofemoral ligament tearing. As in other ligamentous injuries, it can occur due to direct trauma or from sudden change in direction or muscular contractions. It is not unusual for the patella to spontaneously relocate. After radiographs are obtained to document fractures and if the patella remains dislocated, administering an adequate amount of intra-articular anesthesia and gently elevating the patella while providing a medially direct force accomplish the reduction. Postreduction radiographs are recommended. There is invariably an injury to the lateral femoral condyle and the accompanying facet of the patella as the patella dislocates over the lateral femoral condyle. After knee bracing with a patellofemoral brace, all patients should be referred to orthopedics for management as primary repair is recommended for some patient populations.

A complete knee dislocation is a major traumatic event that should be managed in an emergency room/hospital setting similar to a hip dislocation. In addition to the ligamentous and potential osteochondral abnormalities associated with the injury, the integrity of the popliteal artery must be evaluated in all cases.

Lower Leg/Ankle/Foot Injuries

Calf Injuries

General Principles

Injuries to the posterior lower leg (calf) are common, with a higher prevalence of calf injuries in athletes greater than 40 years old [22]. The muscles of the superficial posterior compartment of the lower leg are the gastrocnemius, soleus, and the plantaris. The gastrocnemius and soleus muscles are known as the triceps surae (some anatomists believe they are one muscle with three heads combining at the Achilles tendon to insert on the posterior calcaneus) (see Fig. 5). Together these muscles function as the primary plantar flexor of the ankle. Most injuries to these muscles occur with sudden explosive movements or prolonged impact activities. The gastrocnemius is a biarticular muscle of the lower extremity and is composed of a medial and lateral head originating on their respective femoral condyles. The soleus has a broad origin on the proximal tibia and fibula. Over 90% of injuries in the calf involve only the gastrocnemius muscle, with 86% of those injuries in the medial head, and 14% in the lateral head [23]. The plantaris muscle has significant anatomic variability of its presence and location. When present, it originates just medial to the lateral head of the gastrocnemius and traverses proximally between the gastrocnemius and popliteus muscles and distally between the gastrocnemius and soleus muscles. The function of the plantaris is debated; injury to its muscle or tendon must remain in the differential of calf pain. The popliteus muscle originates from the lateral condyle as a component of the posterolateral corner of the knee and inserts on the posterior aspect of the proximal tibia. Although not a traditional calf muscle, it is included for discussion as it can be a source of pathology in the proximal calf area either due to a tendinopathy or compression of the neurovascular bundle that lies in close approximation to the muscle tendon.

Diagnosis

Gastrocnemius injuries are commonly acute in origin, occurring with explosive or dynamic eccentric loading of the calf with activities such as sprinting or jumping. As an example, a tennis leg is a common injury to the medial head of the gastrocnemius that occurs with knee extension and sudden ankle dorsiflexion. The associated pain of this acute injury is described as a tearing or stabbing sensation, and most patients have difficulty bearing full weight on the injured leg. There may be a variable amount of swelling or

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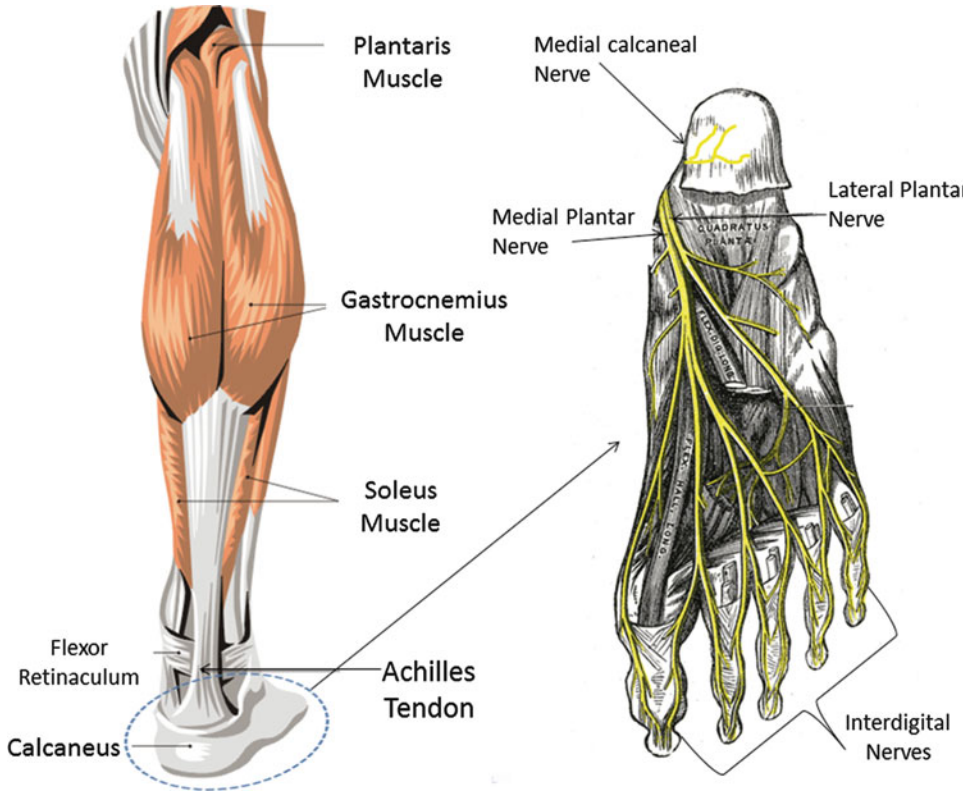


Fig. 5 Posterior distal leg and plantar foot anatomy (distal leg image adapted with permission from fpnotebook.com). Plantar foot adapted from *Gray's Anatomy* 20th edition from 1918 (Lewis) in the public domain following expiration of its patent. Available online at http://bartleby.com/107/)

bruising, depending on the degree of muscle injury. Active plantar flexion of the ankle with the knee extended, and passive or active dorsiflexion of the ankle can reproduce the patient's pain. An isolated or concomitant Achilles tendon tear must be ruled out. Both diagnoses have similar mechanisms of injury but are differentiated by physical exam and imaging. Achilles tendon integrity is assessed with careful palpation to identify a defect despite the considerable swelling around the tear. Also, perform the Thompson squeeze test by placing the patient in the prone position and squeezing the proximal calf musculature. The nomenclature of the Thompson squeeze test can be confusing; a negative squeeze test is when plantar flexion is present, indicating an intact muscle-tendon complex, and a positive test is when plantar flexion is not present, indicating a disruption of the muscle-tendon complex. It is less misleading to describe the motion observed when squeezing the posterior calf as opposed to saying a negative or positive test. Some passive plantar flexion may be present in up to 10% of complete Achilles tendon ruptures from an intact plantaris muscle or activation of the deep posterior compartment muscles of the leg. Likewise, the lack of passive plantar flexion does not indicate a complete tear. Two case reports demonstrate a positive calf squeeze, and upon surgical evaluation, only a tear of the gastrocnemius was identified in the triceps surae [24]. Pursue further imaging with ultrasound or MRI if clinical suspicion remains high for an Achilles tendon injury despite a normal or equivocal physical exam. An ultrasound is the least expensive and rapidly obtained. However it is operator dependent and an intact plantaris can be mistaken for an intact

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Achilles tendon, and a large hematoma can obscure the tear.

Plantaris injuries are commonly acute in origin with the same mechanism of injury as gastrocnemius injuries. Symptoms are similar but not as severe. Swelling and bruising are not always apparent because the plantaris muscle and tendon lie deep to the gastrocnemius. These injuries are usually located in the mid-calf and are more distal to the injuries of the medial head of the gastrocnemius. As the plantaris usually does not contribute to the Achilles tendon, the calf squeeze test will be negative, resulting in passive ankle plantar flexion. An exception to this would be if the Achilles tendon was involved in the acute injury.

Contrary to gastrocnemius and plantaris muscle injuries, soleus muscle injuries characteristically are of a chronic nature. The chronicity of these injuries may occur because the soleus contains predominantly slow-twitch muscle fibers, whereas the gastrocnemius is comprised of both fast- and slow-twitch muscle fibers. Distance runners and those who engage in hill running are more vulnerable to soleus injuries. Palpation of the calf reveals deep muscle soreness and minimal to no swelling or contusion. A functional exam of the soleus muscle can help elucidate the diagnosis by the patient performing active plantar flexion with heel raises on a step with the knee flexed to 20–30°. The gastrocnemius is tested by repeating the functional exam with the knee in full extension. If the patient's pain is exacerbated while the knee is flexed, but reduced or absent with knee extended, this finding is highly suggestive of a soleus muscle injury.

As mentioned earlier in GTPS, a complete physical examination should include the entire kinetic chain looking for leg length discrepancies, pes cavus or pes planus, flexibility deficits, and strength deficits such as hip weakness with the Trendelenburg test (see Fig. 3). Table 4 provides a differential diagnosis for lower leg complaints.

Treatment

Treat these injuries in a phased approach. A detailed description is provided and serves as a model for other muscle or tendon injuries (e.g., groin, quadriceps, and hamstring injuries). The initial phase protects an acute injury from further damage while restoring the range of motion. Calf compression is helpful for posterior calf injuries and accomplished with commercial compression sleeves or elastic bandages; the latter is more prudent to treat an acute injury avoiding neurovascular compression by adjusting the amount of compression. Ice is recommended for acute injuries and utilizes pain medication (i.e., acetaminophen or NSAIDs) as needed. Occasionally severe injuries require modification of weight-bearing with crutches and immobilization, either with a posterior splint or a commercial walking boot. Revisit the need for immobilization and the patient's weight-bearing status every 3–5 days as restoring normal range of motion and their ability to weight bear is essential. Heel lifts can assist in pain relief by shortening the muscle-tendon unit. If a heel lift is used for acute pain management, it should be removed as soon as pain allows, usually 3–5 days, avoiding a permanently contracted muscle-tendon unit.

Once the patient can walk without a limp, test their ability to do a heel lift. If they have minimal pain, the patient may begin the next phase of recovery with active rehabilitation that consists of strengthening the gastrocnemius-soleus complex with repetitive heel raises and progressive loading (see Ref. [9] for home exercises). Plyometric exercises and activity-specific training can begin after the patient can tolerate progressively loading without recurrence of pain or dysfunction. Every patient's injury recovery time is variable. Functional assessments should guide treatment advances to include the ability to walk without a limp, ability to do heel lifts without significant pain, progressive loading, and pain-free functional activity.

The continued use of a calf compression sleeve is an option and patient dependent. To prevent a recurrence, patients should maintain a strengthening program of the lower extremity. The use of foot orthosis can be considered for leg length abnormalities or pes cavus or planus.

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Achilles Tendon Rupture

General Principles

The Achilles tendon has poor vascularity 2–6 cm proximal to its insertion on the calcaneus (see Fig. 5). This watershed area is at risk for tendinopathies and rupture. Men are approximately four times more likely to have an Achilles tendon rupture. The age-adjusted incidence, regardless of gender, peaked at 41 years old with a mean incidence of about 69/100,000/person-year [25]. The mechanism of injury is the same as for acute calf injuries described above, which is a vigorous contraction of the calf muscle with explosive or dynamic movements, while the ankle is in a dorsiflexed position. The exact pathophysiology of an Achilles tendon rupture is unknown, but underlying tendinopathy and impaired blood flow appear to be correlated to this injury. All fluoroquinolones demonstrate an increased risk of Achilles tendinopathy. Ofloxacin and norfloxacin are the only two fluoroquinolones that demonstrate a significant risk of Achilles tendon rupture, and the concomitant use of corticosteroids did not have a significant increase in that risk. After 30 days from the initial exposure to the medication, the risk of Achilles tendon rupture returns to the patient's baseline. The highest risk of Achilles tendinopathy and rupture was seen in those patients 60 years of age and older [26].

Diagnosis

An oft-heard complaint is "someone kicked me in the back of the leg." An audible snap is common, with an antalgic gait and minimal power with push-off, but the patient is otherwise able to compensate with the muscles of the deep posterior compartment and the plantaris muscle. Most complain of intense pain, but a case series demonstrated that up to one-third of patients had no pain with an acute rupture [27]. It is speculated that these patients had chronic tendinopathy, and the rupture relieved the discomfort from tendinopathy. Acutely significant swelling and ecchymosis are usually present. Careful palpation of the tendon will reveal a gap but can be obscured due to the inflammation or a hematoma. As above, the entire calf musculature should be examined to identify gastrocnemius, soleus, or plantaris injuries (see Table 4).

Strength testing demonstrates markedly decreased plantar flexion. The calf squeeze test described above usually demonstrates a positive test with no passive plantar flexion of the ankle. As mentioned earlier, with a complete rupture, plantar flexion may be present, and conversely loss of plantar flexion is not 100% sensitive or specific for a complete rupture. Ruptures are missed in up to 25% of patients due to multiple variables to include a confounding exam. These estimates were made before the widespread availability of ultrasound and MRI. If a tendon rupture is suspected despite a negative or equivocal exam, obtain advanced imaging studies to avoid the high morbidity of a missed rupture.

Treatment

Traditionally, the treatment of Achilles tendon ruptures was surgical for the active population and nonoperative for the elderly or those with significant comorbidities. Recent studies demonstrate that nonoperative treatments are a viable option for active populations when coupled with modern rehabilitation techniques. Nonoperative treatment includes physical therapy combined with progression from non-weight-bearing in a cast or a walking boot to a walking boot with incremental reductions in the height of heel wedges guided by a clinical and radiographic assessment of the tendon integrity. The re-rupture rates are low, and the risk difference between the operative and nonoperative groups is small at 1.6%. The operative group has a 3.3% higher-risk difference of complications (i.e., infection, DVT, wound adhesion) [28]. Early functional rehabilitation within the first 2 weeks of surgery with weight-bearing and various exercise-based interventions is inconclusive because of the high variability and lack of standardization of exercises. However, higher patient satisfaction is demonstrated with the transition from a rigid cast to functional bracing within 2 weeks of surgery [29]. A referral is recommended to an orthopedic surgeon unless the physician has considerable experience in managing Achilles tendon ruptures, including casting

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and splinting. Informed and shared decision-making is paramount to determine the most appropriate treatment course.

Plantar Fasciopathy (PF)

General Principles

Plantar fasciopathy (PF), also known as plantar fasciitis, is the most common cause of heel pain in adults, affecting more than 2 million annually in the United States. The peak incidence is between 40 and 60 years old [30]. Higher-risk populations include runners and occupations with prolonged standing. Physical factors that predispose patients to PF include limited ankle dorsiflexion and obesity.

A complicated fibrous network richly invested with small nerves connects the plantar fascia to the structures of the foot. The plantar fascia consists of medial, central, and lateral bands originating on the plantar aspect of the calcaneus. PF occurs most frequently in the central band, which extends distally dividing into five bands that insert on the metatarsophalangeal joints. Its primary function is to provide both static and dynamic support of the longitudinal arch.

Biomechanical dysfunction leading to microtears at its calcaneal attachment is thought to be the etiology. Plantar fasciitis is a misnomer in most patients because the histopathology of PF reveals degenerative tissue with a lack of traditional inflammatory cells, which directly impacts the treatment options [31]. However enthesopathic conditions such as seronegative spondyloarthropathies can present with pain and inflammation of the plantar fascia due to an autoimmune inflammatory process.

Diagnosis

The classic patient presentation is increased pain upon the first steps after sleeping or prolonged sitting that improves or diminishes in severity after a few minutes of ambulation. Radicular pain is atypical and should alert the physician to an alternative diagnosis such as nerve compression. Perform an inspection of the lower extremity to identify comorbidities or kinetic chain dysfunction to include true or functional leg length abnormalities and foot abnormalities such as pes cavus or planus (see Table 2). Usually swelling or bruising is absent in PF and if present raises the concern for an alternate diagnosis. Physical exam findings include sharp pain and tenderness over the medial plantar calcaneal region which is accentuated with great toe extension and ankle dorsiflexion. Ankle dorsiflexion can be limited due to PF pain and posterior calf tightness. Both of these factors need to be considered as a part of the rehabilitation program. Palpation and percussion of the posterior tibial nerve, especially the medial calcaneal and lateral plantar branches, should be performed to ensure they are not the source of the pain (see Fig. 5).

PF is a clinical diagnosis. Imaging is reserved to rule out other conditions. Plantar calcaneal spurs are present in patients with and without symptoms of PF. The formation of heel spurs is hypothesized to be an adaption to bony stress at the plantar fascia origin on the calcaneus. The most common mimickers of PF are heel fat-pad syndrome and neuropathies, but it is possible to have multiple concurrent pathologies, and one may beget the other [32] (see Table 5 for differential diagnosis).

Treatment

The natural history of PF is a self-limited resolution in about 90% of patients, but this may take up to 12 months. There are a myriad of treatments with limited evidence as well as conflicting and mixed results. Therefore a conservative, least invasive, cost-effective approach is prudent. Obesity is an extrinsic risk factor for musculoskeletal conditions and should be addressed. If training errors are revealed, these should be corrected. If biomechanical dysfunction is discovered, this should be corrected (e.g., lower extremity and core weakness, flexibility deficits, leg length abnormality, pes cavus, or planus) (see Table 2). Initial treatment is aimed at controlling pain to allow normal activities of daily living (ADLs) and then progressing to meet the patient's desired activity goals. In the acute setting, pain relief is the primary goal and can be accomplished with ice massage, oral, topical, or injectable pain

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Table 5 Differential diagnosis of ankle and food disorders of the lower extremity

Very common	Common	Infrequent	Referred
Ankle sprain Plantar fasciopathy Tendinopathy [a] Stress fracture Osteoarthritis	Achilles tendon rupture Fractures Metatarsalgia (multiple causes) Toe abnormality [b] Hallux valgus Interdigital nerve entrapment Corns/calluses Sesamoid disorders	First MTP joint sprain (turf toe) Calcaneal abnormalities (retrocalcaneal, Haglund) Enthesopathies of autoimmune conditions Fat-pad atrophy Nerve compression [c] Osteochondrosis [d] Hallux rigidus Lisfranc injury Plantar fascia rupture Cuboid subluxation Plantar fibromatosis Sinus tarsi syndrome Tarsal coalition	Radiculopathy Chronic regional pain syndrome Septic arthritis Neoplasm Vascular disorders

[a]Achilles, posterior tibialis, peroneal (fibularis), flexor hallucis
[b]Hammer, mallet, claw, curly
[c]Posterior tibial-tarsal tunnel, lateral plantar, medial calcaneal, peroneal (superficial, deep)
[d]Calcaneal (Sever), navicular (Köhler), metatarsal head (Freiberg)

medications. No difference was found in pain or functional outcomes in patients with plantar heel pain, whether they were placed in custom or prefabricated foot orthoses [33]. As tolerated, proceed with the stretching and strengthening of the foot and lower extremity. In addition to plantar fascia stretching, the triceps surae should be stretched (see Ref. [9] for home exercises). Standing with just the toes on a step or placing a towel under the toes while performing heel raises with the eccentric lowering of the heel into dorsiflexion stretches both the Achilles tendon and plantar fascia and is a form of eccentric loading and strengthening. Eccentric strengthening occurs when the muscles are lengthened while contracting to control the dorsiflexion of the ankle and has shown to have superior outcomes to corticosteroid injections into the plantar fascia [34]. No evidence-based recommendations can be made for orthoses such as counterforce braces, socklike sleeves, or dorsiflexion splints, but some patients demonstrate anecdotal improvement with their use. These orthoses should not be used in isolation but as part of a comprehensive treatment regimen that includes stretching, strengthening, and the correction of extrinsic risk factors.

Consider injection therapies for refractory cases of chronic PF. Corticosteroids combined with an anesthetic can provide immediate short-term relief after the injection and can help to confirm the source of pathology. Their repeated use is discouraged for the risk of fat-pad atrophy or plantar fascia rupture. In general, utilize this treatment for severe pain that limits ADLs or restricts rehabilitation. Injection therapies with prolotherapy, PRP, and botulinum toxin are options for recalcitrant cases with varying levels of evidence. Low-frequency shock wave therapy treatments may have a role in the treatment of PF when other conservative measures fail, but patient outcomes are mixed in the literature. Surgery is a last resort, and the diagnosis must be revisited if the patient is not responding to other treatments.

Metatarsalgia

General Principles

Metatarsalgia is pain at the metatarsals, which is a nonspecific term for any painful condition around the forefoot, generally at the metatarsal heads. It is a symptom rather than a condition, and the treatment is determined by identifying the underlying cause (i.e., the victims and culprits concept discussed in GTPS). The first digit absorbs 40% of impact forces of the foot. Any condition that alters this force distribution can contribute to

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metatarsalgia. The second metatarsal head is affected more often due to its relative inflexibility when compared to the other digits, its proximity to the main force absorber (i.e., the first digit), and a common anatomical variant of a shortened first metatarsal [35]. The following section will discuss common causes of metatarsalgia in greater detail with a more extensive list in Table 5.

Diagnosis

Metatarsalgia has a gradual onset of pain without trauma. Obtaining an occupational history can identify modifiable risk factors. Inquiring about recent exercise patterns is paramount because a delayed diagnosis of a stress fracture can result in significant morbidity (see Table 2 for risk factors). Inspect the entire kinetic chain for apparent abnormalities. Local tenderness is present with palpation of the plantar metatarsal heads. Weight-bearing plain radiographs may be ordered to assess for additional bony pathology. Utilize advanced imaging with ultrasound and MRI to evaluate for other pathologies (e.g., stress fractures, neuralgia, and sesamoiditis). Salient findings for the specific diagnosis will be discussed under their respective sections.

Treatment

Successful long-term treatment resides with identifying the cause of the patient's symptoms. For generalized metatarsalgia without a specific etiology, a metatarsal pad or bar can be used to off-load the metatarsal heads. If the patient has noticeable anatomic changes, consider a custom foot orthotic.

Interdigital Nerve Compression

A variety of conditions cause compression and swelling of the interdigital nerves of the toes (see Fig. 5). A Morton's neuroma, which is actually a neuritis and not a true nerve tumor, occurs most commonly between the third and fourth digit. Paresthesias can be present and amplified with direct palpation along the nerve's distribution. Compression of the metatarsal heads by squeezing both sides of the forefoot can cause the affected interdigital nerve to have a painful click or snap between the two opposing bones (i.e., Mulder's sign).

Symptomatic relief with an anesthetic block can be diagnostic and if combined with a corticosteroid, therapeutic. A dorsal approach is highly recommended to avoid complications. Ultrasound guidance is advocated to ensure precise delivery under direct visualization. Recurrence can be treated with either chemical or surgical nerve ablation techniques, but successful long-term management includes correction of the biomechanical causes of nerve compression.

Sesamoiditis

Sesamoiditis is a generic term for pain located around the sesamoid complex of the foot. The sesamoid complex absorbs the most force for the first ray. There are two sesamoid bones embedded, respectively, in the lateral and medial heads of the flexor hallucis brevis at the first MTP joint. They function to improve the power of flexion at the MTP joint and to absorb the majority of forces along the medial aspect of the foot. Either sesamoid can be bipartite, and patients with pes cavus have a higher risk for sesamoid injuries [36].

Patients present with pain upon palpation of the affected sesamoid and with great toe dorsiflexion. Treatments include correcting biomechanical dysfunction and redistributing impact forces at the sesamoids with various types of padding (e.g., dancer's pads) and foot orthoses. Imaging is not required unless the diagnosis is uncertain or the patient is not responding to conservative treatments. If required plain films, including an axial sesamoid view, can be challenging to interpret. An MRI is more definitive as it will reveal the presence of stress fractures, soft tissue swelling, or other concomitant pathology. The differential diagnosis for the athletic population includes first MTP joint sprain or turf toe. Turf toe is an acute injury that can be recalcitrant to healing, as it is difficult to unload this area entirely. It is frequently treated with rest and custom orthoses.

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Distal Tibia/Fibula/Ankle/Foot Fractures

Acute fractures of the ankle are common but usually present with the same mechanism as an ankle sprain which is discussed in ▶ Chap. 55, "Athletic Injuries." The foot and leg are the most common locations for stress fractures because of the high, repetitive force loads imparted. As mentioned earlier, they are preceded by new mechanical stresses for which the body has not had time to accommodate. See Table 3 for low- and high-risk stress fractures and management.

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Osteoarthritis

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General Principles

Definition/Background

Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage deterioration and hypertrophy of bone. OA can present in almost any joint in the body, but the knee is the most common location to develop this condition [1]. Other common locations include the fingers, hips, and spine. OA develops when degeneration exceeds chondrocyte remodeling leading to cyst formation, further cartilage loss, and decreased joint use that further decreases the physiologic stimulation of chondrocyte activity. OA threatens patients' ability to participate in healthy physical activity, thereby predisposing them to increased cardiovascular disease, weight gain, diabetes, and potential loss of independence [2].

Epidemiology

OA is one of the most common chronic medical conditions and the most common type of arthritis [1]. In 2020, the Centers for Disease Control reported that OA affects over 32.5 million US adults [3]. Estimated costs from hospital expenditures due to joint replacement surgery in 2013 accounted for $16.5 billion, or 4.3% of the combined costs for all hospitalizations in 2013 [3]. For privately insured patients, OA was the most expensive hospitalized condition amounting to over $6.2 billion in hospital costs [3]. Risk factors include genetics, acute or recurrent trauma, advancing age, female gender, and obesity [4].

Classification

In 1981, the American College of Rheumatology (ACR) organized a subcommittee to develop criteria to better define OA [5]. The committee developed two methods of classification: traditional inclusion criteria and classification trees. A superior approach according to the ACR is using the tree model in which the appropriate tree is utilized based on patient data. Although clinical data is sufficient to diagnose OA, laboratory and radiographic data may improve sensitivities and specificities. The three joints evaluated were the knee, hip, and hands. There are several classification schemes for OA but the ACR is the most widely used.

Osteoarthritis of the Knee

Traditional inclusion criteria of the knee developed in 1989 include knee pain plus at least three of the following six clinical characteristics: greater than 50 years of age, morning stiffness for less than 30 min, crepitus on active motion of the knee, bony tenderness, bony enlargement, or no palpable warmth. Using these criteria, there is a sensitivity of 95% and specificity of 69% in diagnosing OA [5].

Knee osteoarthritis classical clinical criteria [5]

- Knee pain
- Plus at least three of the following
  - Greater than 50 years old
  - Morning stiffness for less than 30 min
  - Crepitus on active motion of the knee
  - Bony tenderness
  - Bony enlargement
  - No palpable warmth

Using the classification and regression tree technique (CART), three trees were formed for knee OA. The first tree was based on clinical features alone, clinical features with laboratory findings, and combined clinical, laboratory, and radiographic features. Sensitivities for these trees were 89%, 88%, and 94%, respectively, and specificities were 88%, 93%, and 88%, respectively [5].

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Osteoarthritis of the Hip

The traditional inclusion criteria for diagnosing OA of the hip developed in 1991 include hip pain plus at least two of the following features: erythrocyte sedimentation rate (ESR) of less than 20 mm/h, radiographic osteophytes (femoral or acetabular), or joint space narrowing on radiography (superior, axial, or medial). These criteria accurately diagnose OA with a sensitivity of 89% and specificity of 91% [6].

Hip osteoarthritis classical clinical criteria [6]

- Hip pain
- Plus at least two of the following
  - Erythrocyte sedimentation rate of less than 20 mm/h
  - Radiographic osteophytes (femoral or acetabular)
  - Joint space narrowing on radiography (superior, axial, or medial)

Two classification trees were developed for the hip. The trees were made with and without radiographs. The tree that did not incorporate radiographic features included internal rotation of less than 15°, pain on internal rotation, morning stiffness, age, ESR, and flexion of less than 115°. This tree had a sensitivity and specificity of 86% and 75%, respectively. With the addition of radiographs assessing for radiographic osteophytes and axial space narrowing, the sensitivity and specificity improved to 91% and 89%, respectively [6].

Osteoarthritis of the Hands

Traditional inclusion criteria for OA of the hands developed in 1990 include hand pain (including hand aching or stiffness) plus at least three of the following: hard tissue enlargement of two or more of ten selected joints (second and third distal interphalangeal (DIP) joints, the second and third proximal interphalangeal (PIP) joints, and the first carpometacarpal (CMC) joint of both hands), enlargement of two or more DIP joints, fewer than three swollen metacarpalphalangeal (MCP) joints, and deformity of at least one of the ten selected joints. These traditional inclusion criteria yielded a sensitivity of 94% and specificity of 87% [7].

Hand osteoarthritis classical clinical criteria [7]

- Hand pain (including hand aching or stiffness)
- Plus at least three of the following
  - Hard tissue enlargement of two or more of ten selected joints (second and third distal interphalangeal joints, second and third proximal interphalangeal joints, first carpometacarpal of both hands)
  - Hard enlargement of two or more distal interphalangeal joints
  - Fewer than three swollen metacarpophalangeal joints
  - Deformity of at least one of the ten selected joints

Classification trees with and without radiographic features were created and found to be identical in that there was no statistical difference in the inclusion criteria. The sensitivity and specificity of the two trees were 92% and 98%, respectively. As a result, hand OA is often classified by only clinical features [7].

Approach to the Patient

OA is most likely seen in the older patient with insidious onset of pain, swelling, and morning stiffness in the affected joints. History and physical exam can guide a primary care provider's suspicion for OA. Consider an alternate diagnosis in the presence of acute pain, swelling, erythema, fever, or rash. Radiologic and laboratory studies may also be necessary if an alternate diagnosis is suspected.

Diagnosis

History

OA is often diagnosed by an overall clinical picture using the patient's age, history, physical examination, and radiographic findings. No single clinical feature is absolutely sensitive or specific in making the diagnosis. Patients initially present

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Table 1 X-rays for osteoarthritis [11]

Knee	Anteroposterior weight bearing, lateral, oblique
Hip/pelvis	Anteroposterior weight bearing
Spine	Anteroposterior, lateral
Hand	Anteroposterior, lateral, oblique, magnified view
Foot	Anteroposterior, lateral, oblique, magnified view

with symptoms to include pain, limited morning stiffness, and reduced function [8].

Physical Examination

Some common signs include crepitus, joint swelling, restricted movement, and bony enlargement [8]. In later stages, joint deformity may be present [8]. Erythema, fever, severe local inflammation, and progressive pain may suggest another diagnosis [8]. In the presence of an effusion, consider aspiration and fluid analysis.

Laboratory and Imaging

According to the European League for Rheumatism, three symptoms (persistent knee pain, limited morning stiffness, and reduced function) and three signs (crepitus, restricted movement, and bony enlargement) in a patient with risk factors for OA can make the diagnosis, and imaging may not be necessary. With all six of these factors present, the probability of seeing OA on a radiograph is 99% [8]. Laboratory tests and radiographs are not needed to accurately diagnose OA, but testing may rule out the likelihood of another process occurring. Radiographic findings may be misleading and disproportionately severe when compared to pain or the clinical examination.

Laboratory tests are typically normal for uncomplicated osteoarthritis. White blood cell count derived from synovial fluid would be expected to be less than 2,000 per mm ^{3} (2.0×10^9 per L) [9].

Radiologic abnormalities that are often present include joint space narrowing, osteophytes, and subchondral sclerosis [10]. For the evaluation of knee OA, a weight-bearing anteroposterior, lateral, and oblique views should be ordered. For the evaluation of hip/pelvis OA, an anteroposterior weight-bearing film should be ordered. For the evaluation of spine OA, an anteroposterior and lateral film should be ordered. For the evaluation of hand OA, an anteroposterior, lateral, and oblique film should be ordered. A magnified view of the specific joint may also be beneficial. For the evaluation of foot OA, an anteroposterior, lateral, and oblique film should be ordered. A magnified view of the specific joint may also be beneficial (Table 1) [11].

Differential Diagnosis

The differential diagnosis for OA includes crystal-induced arthritis, gout, pseudogout, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, septic joint, osteoporosis, metastatic cancer, multiple myeloma, scleroderma, Reiter's syndrome, systemic lupus erythematosus, and Lyme disease.

Treatment

The treatment of OA is directed towards reduction of symptoms and preventing disability. To manage the symptoms of OA, patients and healthcare providers often consider multiple approaches [1]. Although there are no pharmacologic therapies that prevent the progression of joint damage due to OA, many medications may help alleviate the symptoms. The goal of therapy is to control pain and swelling, minimize disability, and improve quality of life.

Lifestyle Modifications

Nonpharmacologic treatment of OA should be the cornerstone to management and should be tried first, followed by pharmacologic augmentation to

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relieve pain when necessary. Symptoms of OA are typically relieved with rest; however, resting the affected joint may lead to muscle atrophy and decreased joint mobility. Rest is only recommended for a short period of time (typically 12–24 h for acute pain) after which active and passive joint motion and exercises should resume.

Alternatively, high and low intensity aerobic exercises are beneficial for improvements in functional status, pain, gait, and aerobic capacity [12]. Exercising also decreases the incidence of obesity which is strongly associated with the development of OA. The relative risk of developing knee OA in patients with a high BMI (no specific BMI) was 1.5 for men and 2.1 for women [13]. In a follow-up study using the same population, the risk of developing OA was reduced following weight loss. A 10 lb. weight loss over 10 years reduced the probability of developing knee OA by 50% [14]. Given these implications, weight loss is recommended to help treat and prevent worsening of OA.

Medications

Topical Medications

Topical NSAIDs or capsaicin can be used as treatment in patients with mild disease, who cannot tolerate oral agents, have contraindications to oral agents, or those that may have an increased risk of adverse side effects. Topical NSAIDs can sometimes provide only modest or short-lived benefit and capsaicin may cause local irritation. There are no trials that directly compare topical therapies. Topical NSAIDs may be helpful for the treatment of OA of the hand or knee [15]. Capsaicin has shown mild to moderate efficacy in randomized trials in hand and knee OA in comparison with placebo [16].

Acetaminophen and Anti-Inflammatories

Oral medications are often the mainstay treatment used to treat OA [1]. Acetaminophen is no longer considered first line for OA as evidence has shown that nonsteroidal anti-inflammatory drugs (NSAIDs) are superior for improving knee and hip OA (15). There are certain subsets of patients where acetaminophen may be considered over NSAIDs to include patients older than 65 years and those with an increased bleeding risk. Acetaminophen, if chosen, should be started initially on an as-needed basis, but in patients with persistent symptoms, regular use may be initiated at doses up to 4 g/day [17]. Acetaminophen is generally safe but hepatotoxicity can occur at high doses, especially in patients who concurrently are at risk for hepatic function impairment due to lifestyle choices, polypharmacy, or underlying pathophysiology. In patients who take acetaminophen on a chronic daily basis, consider laboratory testing to assess for hepatotoxicity.

Nonsteroidal anti-inflammatory drugs work by preventing inflammation and controlling pain by blocking cyclooxygenase (COX-1 and COX-2 enzymes) [1]. The side effect profile of NSAIDs is not always favorable, and each year, more than 100,000 patients are hospitalized for gastrointestinal complications resulting from NSAID use with 15% of these patients dying from these complications [1]. NSAIDs should be avoided in patients with prior gastrointestinal ulcers or bleeding and in patients who are taking anticoagulants [18]. Inhibition of the COX-1 enzyme is responsible for the associated gastrointestinal toxicity [18]. In addition, NSAIDs are limited in patients with cardiovascular and renal complications. The choice of an NSAID is based upon a variety of factors, and there is no convincing evidence that any of the available NSAIDs are more effective than any other for OA of the knee or hip [19]. A short to medium acting NSAID is generally used on an episodic basis in patients with non-inflammatory OA. In inflammatory OA, longer therapy at a higher dosage may be required to control symptoms. If one NSAID is not effective after 2–4 weeks on a maximal dosage, then consider the use of a different NSAID. Aim to use NSAIDs on an as needed basis at the lowest dose required to control the patient's symptoms. COX-2 inhibitors were developed to provide relief of pain without associated gastrointestinal

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complications; however, COX-2 inhibitors have a similar risk of serious adverse gastrointestinal effects as other NSAIDs in long-term users [18]. Chronic use of COX-2 inhibitors has also been associated with an increased cardiovascular risk [18]. Consider treating gastrointestinal symptoms associated with NSAID use with antacids, H2 blockers, or preferably proton pump inhibitors. In patients being treated chronically with daily NSAIDs, consider obtaining a complete blood count, blood urea nitrogen, creatinine, and aspartate aminotransferase.

Intra-Articular Injections

Intra-articular injections are common treatments for OA patients with moderate to severe pain that is not adequately controlled by oral medications. Clinical evidence suggests that the benefit is short lived, and usually patients report symptoms returning after 1–4 weeks [20]. Corticosteroids are proven to be effective at reducing pain in knee OA, although duration and efficacy of these treatments is controversial [2]. Corticosteroids decrease pain by roughly one third, but provide that benefit for only approximately 1 week [2, 20]. A dose equivalent to 50 mg of prednisone may be required to show benefit at 16–24 weeks [20]. The ACR suggests that a dose of 40 mg triamcinolone be used for injections to provide adequate pain relief [20]. Triamcinolone appears to be more efficacious than either methylprednisolone or betamethasone [2]. There is concern that long-term treatment could promote joint destruction and tissue atrophy; however, studies tend to suggest that changes are more likely due to the underlying disease than the steroid injection [20]. It is recommended that the same joint not be treated more than four times a year. Intra-articular glucocorticoid injections are generally well-tolerated and septic arthritis is rare.

Hyaluronic acid is a secondary medication option for intra-articular injections. In long-term studies of patients with symptomatic hip degenerative joint disease, however, intra-articular injection of hyaluronic acid was no better than placebo [21]. In a Cochrane review, hyaluronic acid and hylan products were found to be superior to placebo in efficacy; however, the sample size was small and many different types of viscosupplementation were used. The study found beneficial effects on pain, function, and patient global assessment especially at the 5- and 13-week post-injection period. In some analyses, viscosupplements were comparable in efficacy to systemic forms of treatment but with more local reactions and fewer systemic side effects [22]. The use of these medications remains controversial.

Opioids

In patients with significant OA symptoms not adequately treated with acetaminophen, NSAIDs, or joint injections, a low potency opioid analgesic may be considered. Tramadol is a weak opioid that does not produce gastrointestinal bleeding or renal problems. A Cochrane review showed that tramadol or tramadol/paracetamol decreased pain intensity, produced symptom relief, and improved function, but these benefits were small [23]. Adverse events were not shown to be life threatening, and the drug may have had some synergistic effect with acetaminophen [23]. It is recommended not to use nontramadol opiates due to the increased risk for adverse events [24].

Other Pharmacologic Options

In patients with OA in multiple joints, who may not be able to tolerate NSAIDs, or who have not responded satisfactorily to other interventions, duloxetine can be considered. Duloxetine works on desensitizing central nociceptive processing through selective inhibition of serotonin and norepinephrine uptake. At doses of 60 to 120 mg daily, duloxetine was found to have a relative risk of 30 and 50% improvement in pain intensity of 1.49 (95% CI 1.31–1.70) and 1.69 (95% CI 1.27–2.25), respectively, for knee OA compared to placebo after 10 to 13 weeks of treatment [25]. Medication side effects included constipation, diarrhea, dizziness, dry mouth, fatigue, and

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somnolence. Gabapentin at a dose of 600 mg daily similarly was shown to reduce pain and improve functional status in patients with knee OA but this medication took longer than traditional therapy to work, around 3 months [26]. It had similar side effects to the duloxetine.

In patients with moderate to severe OA of the hip or knee and inadequate response to standard therapy, tanezumab was shown to significantly reduce pain and improve function in comparison to placebo but there was also an increase in total joint replacements following treatment [27]. As a monoclonal antibody which inhibits nerve growth factor binding and reduces pain hypersensitivity, further research is needed to determine the clinical significance of its efficacy and adverse effect profile.

Referrals

Consider referring patients for assistive devices or braces if patients have restrictions of their activities of daily living. Occupational therapy may be helpful for hand-related or specific work issues. Physical therapy may be helpful for all other patients with the exception of hip osteoarthritis. A recent study in 2014 showed that physical therapy was no more effective than sham therapy in reducing pain and improving function in adults with hip osteoarthritis [28].

Complementary and Alternative Therapy

Controversy exists about the effectiveness of glucosamine, chondritin, vitamin D, diacerein, avocado soybean unsaponifiables, and fish oil. In some studies, glucosamine was found to reduce the pain of moderate to severe OA of the knee to improve function and slow the progression of joint space narrowing with an onset of benefit at 4 weeks [29, 30]. A Cochrane review found that some formulations of glucosamine (as a Rotta brand pharmaceutical preparation) were effective in improving OA symptoms but non-Rotta preparations were shown to be ineffective [29]. Due to clear lack of evidence, this should not be routinely recommended.

Other complementary therapies such as curcumin, *Boswellia serrata,* ultrasound therapy, acupuncture, magnet therapy, ginger, leaches, laser light therapy, platelet-rich plasma, dextrose prolotherapy, tai chi, balneotherapy, autologous chondrocyte implantation, and ice massage may be helpful in treating OA but there is limited evidence [31–43].

Surgical Options

Surgical options are often last-line therapy for OA. Joint replacement should be considered for patients with restriction of joint mobility, weekly exertion-induced pain that restricts exercising, or severe OA; however, the final treatment decision should be made individually [44]. Arthroscopy with arthroscopic debridement and lavage is not an effective treatment for OA of the knee [45]. In one randomized control trial (RCT), arthroscopic surgery plus medical and physical therapy was no more effective than medical and physical therapy alone [46]. Obese patients with BMI >30 are no longer considered as great a risk of hardware failure after total joint replacement as previously thought [44].

Special consideration and optimization of medical therapy should be considered prior to surgical options. Refer to an orthopedic surgeon if pain persists despite continued medical management.

Patient Education and Activation

Patients should be educated on this chronic condition that worsens over time. They should know common symptoms of OA and those symptoms that may lead to a different etiology. Patients should try to control pain primarily with oral medications and may need to escalate care depending on the severity of their symptoms. They should be given references on where to obtain more information.

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Prognosis

Further degeneration of the joint is likely to progress with aging. Obesity and weight gain will lead to further stress and destruction of the joint. Progression is most strongly associated with age, joint space width, femoral head migration, femoral osteophytes, bony sclerosis, Kellgren/Lawrence hip grade 3 (x-rays with moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of the bone contour), baseline hip pain, and Lequesne index score ≥ 10 (a scoring system developed to assess severity of OA, ≥ 10 is considered severe) [47].

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Rheumatoid Arthritis and Related Disorders

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Joint pain is a common complaint in primary care. Pain can be considered acute (days), subacute (weeks), or chronic (generally lasting more than 3 months). Accurately diagnosing the cause of joint pain, encouraging continuity of care, and working with multidisciplinary teams using the right blend of therapeutic modalities give patients the best chance for good long-term outcomes. This chapter will focus, in particular, on diseases that commonly present with joint pain.

Differential Diagnosis of Joint Pain

Step 1: A Thorough Medical History

The key step in diagnosing any of the arthritides is a careful history. By definition, arthritis is acute or chronic inflammation of a joint often accompanied by swelling, erythema, and warmth within any individual joint. Most commonly, arthritis presents with some degree of joint pain. A careful medical history allows for determination of inflammatory and mechanical (degenerative) joint disease.

The history should pinpoint the exact location of the pain. Is the problem limited to one joint (monoarticular), several joints (oligoarticular), or many joints (polyarticular)? Is the problem limited to small joints, large joints, or both? Is the pain truly within the joint? If the pain surrounds the joint (periarticular), this leads to suspicion for soft tissue inflammatory conditions (tendinopathy, bursopathy, enthesopathy). If the pain is more diffuse, systemic disorders come to mind. Is the pain symmetric? Rheumatoid arthritis, systemic lupus erythematosus, polymyositis, Sjögren's syndrome, and scleroderma are commonly polyarticular and symmetric. Other conditions that tend to be polyarticular and asymmetric include psoriatic arthritis, ankylosing spondylitis, and other spondyloarthropathies. Joint stiffness, reduced joint range of motion, swelling, constitutional symptoms (fever, chills, sweats, weight loss), local or generalized weakness, a history of trauma or injury, and the presence of fatigue are other important elements of the medical history. It is important to also define exacerbating and alleviating factors as well as the extent, timing, and waxing/waning nature of symptoms.

The history will help determine to what degree joint complaints are associated with rest and physical activity. Symptoms that are exacerbated by physical activity suggest a mechanical component (particularly when combined with locking or a "give-way" sensation). Morning stiffness describes joint stiffness after a period of generalized inactivity (e.g., overnight sleep). While many individuals can be "slow to get going" in the morning, stiffness lasting for more than an hour is not normal and suggests a systemic inflammatory disease. Patients with degenerative disease, such as osteoarthritis, will more commonly complain of stiffness as the day progresses. Non-inflammatory joint pain typically increases with physical activity. Other historical features supporting an inflammatory component to the joint pain include midday fatigue and joint swelling. A sleep history is important as many patients describe significant interruptions to their sleep habits associated with many of the arthritides. Assessing activities of daily living provides good insight into functional limitations. Asking about tasks such as standing from a chair without assistance, showering, washing, or combing hair and the ability to climb stairs is helpful. Determining how the pain has limited the patient's overall ability to function helps to establish a baseline and determine realistic treatment goals. A thorough past medical, surgical, travel, and occupational history provides additional clues into the source and etiology of the joint pain.

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Step 2: Physical Examination

Everyone presenting with joint pain should have a thorough physical examination that focuses on the musculoskeletal system while looking for systemic clues in all major organ systems such as the skin. The vital signs should be reviewed. A general physical exam can provide clues to systemic illness. Skin lesions, organomegaly, lymphadenopathy, pulmonary or cardiac auscultatory changes, and neurological findings all point to different etiologies of joint pain. Observe the patient's gait. Look for obvious deformities or muscular atrophy. Palpate individual joints for synovial thickening, fluctuance, or laxity. Note passive and active ranges of motion, particularly of the affected joints. Passive range of motion (ROM) is often greater than active ROM in arthritic joints. Test strength and sensation. An accurate documentation of the physical examination, particularly the musculoskeletal exam, is time-consuming but is important to assess changes over time. Utilize any electronic medical record system embedded templates if available. Formal dynamometry can be used to track changes in strength over time (e.g., grip strength).

A thorough history and physical examination should lead (in most cases) to a short list of diagnostic possibilities. Based on the history and examination, laboratory and radiographic studies help pinpoint the final diagnosis and guide appropriate treatment.

Rheumatoid Arthritis (RA)

Background and Pathophysiology

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that affects synovial joints in a symmetric distribution. In most patients without proper therapy, RA is chronic and progressive. Early diagnosis and treatment is important to improve long-term outcomes and potential remission. Early treatment, optimally within 12 weeks of symptom onset, with disease-modifying antirheumatic drugs (DMARDs) gives the best chance of achieving remission [1]. RA occurs in all racial and ethnic groups and is seen more commonly in women (3:1) [2]. Prevalence estimates suggest 1.5 million US adults are affected by RA [3]. First-degree relatives have a twofold to threefold higher risk for developing RA. The disease occurs in all age groups but is more common with increasing age and peaks between the fourth and sixth decades of life. The leading cause of death in RA is cardiovascular disease, and overall mortality is 2.5 times higher in patients with RA as compared to the general population [4].

The definitive cause of RA is unknown. In susceptible individuals, an external trigger, such as infection or trauma, triggers an autoimmune cascade that results in joint inflammation, synovial hypertrophy, joint destruction, and potentially other extra-articular manifestations. A history of parental substance abuse is associated with an increased risk for developing RA in adulthood [5]. Sixty percent of patients with RA in the United States share an epitope on the HLA-DR4 cluster, suggesting some element of genetic risk [6]. Several other genes have weaker associations with RA but may contribute. Following an environmental insult, synovial cell hyperplasia and endothelial activation lead to progressive inflammation with articular damage and bony destruction. Abnormal cytokine and inflammatory mediator production along with activation of both T-cell and B-cell lineages contribute to the pathophysiology of RA. The proliferation of synovial cells and subsynovial vessels leads to synovial proliferation, pannus formation, and articular destruction.

Clinical Presentation

The hallmark presentation of RA involves a persistent, symmetric small joint polyarthritis of the hands, wrists, and feet. In decreasing frequency, the knee, shoulder, ankle, cervical spine, hip, and elbow can also be involved (as can, theoretically, any synovial joint). Most patients have an insidious onset over weeks to months. Morning stiffness is common, and patients report increasing difficulty with routine activities of daily living

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such as personal hygiene, dressing, and combing their hair. Constitutional symptoms (low-grade fever, malaise, fatigue) are common as well. Large joints often become symptomatic later in the course of the disease. The small joints of the hands and feet should be carefully examined for swelling, warmth, tenderness, and changes in range of motion (ROM). Interosseous muscular atrophy is a common early finding. With progressive joint destruction, characteristic joint deformities (such as boutonniere, swan neck, ulnar deviation, or hammertoe) develop. Rheumatoid nodules can develop particularly along the extensor surface of the ulna. Knee effusions are relatively common in RA and may contribute to progressive muscular atrophy of the quadriceps with resulting instability. The hips and cervical spine are also commonly involved in RA. Atlantoaxial instability is more common in patients with early and severe arthritis of the hands and in those on high doses of corticosteroids.

Because RA is a systemic inflammatory process, most patients will exhibit extra-articular manifestations of the disease. Malaise and fatigue are the most common systemic symptoms. Rheumatoid nodules occur in 25% of RA patients. Cardiovascular disease is more prevalent in RA patients. RA is also associated with pericardial effusions, pericarditis, myocarditis, and coronary arteritis. Hematologic malignancies such as non-Hodgkin's lymphoma are more common in patients with RA. Pulmonary complications include pleural effusions, pulmonary fibrosis, nodular lung disease, and bronchiolitis obliterans. RA is also associated with secondary Sjögren's syndrome.

Diagnosis

The diagnosis of RA is based upon the combination of clinical, laboratory, and radiographic findings. In 2010, the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) developed classification criteria to assist in the early detection of RA [7]. This classification represents an update to the 1987 ACR classification criteria as an attempt to better identify patients early in the course of the disease and initiate effective treatment. According to the ACR/EULAR guidelines, patients who have one joint with definitive synovitis that is not explained by another disease process should be tested for RA (Table 1).

Table 1 2010 ACR-EULAR classification criteria for rheumatoid arthritis [7]

	Score
A summative score of 6/10 from elements A through D is consistent with RA	
(A) Joint involvement	
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
(B) Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
(C) Acute phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
(D) Duration of symptoms	
<6 weeks	0
6 weeks	1

Laboratory and Imaging Studies

Selected laboratory tests, undertaken after a careful history and physical examination, can help confirm the diagnosis of RA. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are markers of inflammation. Both are typically elevated in RA. CRP also corresponds over time to radiographic progression of RA. Common complete blood count (CBC) findings associated with RA include an anemia of chronic disease (normochromic, normocytic) and thrombocytosis. Autoantibodies, including rheumatoid factor (RF), antinuclear antibody (ANA), and anticitrullinated protein antibodies (ACPA; tested commonly as anti-CCP), are normally the most

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helpful laboratory tests to aid in the diagnosis of RA. Anti-CCP antibodies have a sensitivity and specificity equal to (or better than) RF for the diagnosis of RA [8]. Patients without RA but who have elevated anti-CCP levels may be at risk of progression to RA [9]. The presence of both anti-CCP and RF is highly specific for the diagnosis of rheumatoid arthritis. As with RF, the presence of anti-CCP antibodies indicates a worse disease prognosis.

Plain radiographs are the preferred initial images in RA. Plain films can show erosions and can be followed serially to mark disease progression. Magnetic resonance imaging (MRI) provides more accuracy and allows for earlier detection of joint changes. MRI is much more costly and is typically used to assess abnormalities of the cervical spine. While ultrasonography is rapidly growing in use for musculoskeletal imaging, its role in RA is evolving. Ultrasound can identify joint effusions in deep joints such as the hip or shoulder and can identify synovial vascularization. As an office-based technology, ultrasonography offers promise in the evolving care for RA patients [10].

Treatment

Successful treatment of RA includes a multidisciplinary, interprofessional team employing a variety of modalities including diet, exercise, stress management, physical therapy, behavioral health, medications, and (potentially) surgery. Patient-centered care focusing on specific treatment goals, patient and family education, and long-term expectations facilitates success.

Nonpharmacologic Treatment

Multiple nonpharmacologic modalities are available to help relieve pain, improve function, and maintain (or enhance) strength and range of motion in patients with RA. The application of heat is effective to relieve pain and stiffness. Hot packs, paraffin baths, ultrasonography, and other modalities may provide relief and also help to prepare affected joints for range of motion and strengthening exercises. Orthotic devices and splints also play an important role in managing patients with RA. These devices can reduce pain, enhance function, reduce deformity, and provide proper mechanical joint alignment. Since most RA patients complain of fatigue and reduced cardiorespiratory endurance, a program of therapeutic exercise is important to maintain aerobic capacity and muscular strength. Involving occupational therapists, physical therapists, and exercise scientists can help provide individualized programs of splinting and exercise prescription to optimize physical function while mitigating the risk of injury.

Pharmacologic Therapy

Multiple medication options exist for the treatment of RA. These options include nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) including biologics, corticosteroids, and non-biologic agents. Selecting the right therapy for the right patient to optimize outcome while minimizing toxicity can be challenging. Therapy with DMARDs should utilize a treat-to-target approach with a goal to reduce disease activity by 50% within 3 months and achieve remission or low disease activity within 6 months [6]. If initial DMARD therapy has not reached target, then alternative therapy should be considered.

NSAIDs and Corticosteroids

NSAIDs and corticosteroids are typically used to provide pain relief and reduce inflammation as a "bridge" for the 3–6 months before DMARD therapy takes effect [11]. NSAIDs do not alter or slow joint destruction and are insufficient monotherapy for RA.

DMARDs

Once the diagnosis of RA has been made, the goal is to control the disease activity, slow joint damage, provide symptomatic relief, and improve overall patient function. The DMARDs and biologic agents are most effective in accomplishing these goals. Vaccination requirements should be administered for patients who are being considered for therapy with DMARD or biologic

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therapy. The recommendations vary slightly depending on the drug being considered. It should be noted that while patients on prednisone and other immunosuppressive agents can and should receive inactivated vaccines, their protective antibody response might be blunted. Every patient should be screened for hepatitis B and hepatitis C infections or latent tuberculosis before starting DMARD or biologic therapy as the therapies may reactivate the disease.

DMARDs can be classified as biologic and nonbiologic agents. Common nonbiologic DMARDS include hydroxychloroquine (HCQ), sulfasalazine (SSA), azathioprine (AZA), methotrexate (MTX), and leflunomide. For treating RA, MTX and SSZ are generally recognized to be the most active with the best risk-benefit ratios. MTX is typically used alone, or in combination with other medications, for moderate to severe RA and can be administered either orally or subcutaneously. The biologic DMARDS include five tumor necrosis factor alpha (TNF-α) inhibitors: etanercept, infliximab, golimumab, certolizumab, and adalimumab. Biologic DMARDs are typically reserved for use when nonbiologic DMARD (e.g., MTX) has not induced a remission or as initial therapy if a patient has many poor prognostic indicators to include erosive disease, positive serological markers, and extra-articular manifestations. Patients on anti-TNF-α therapy should avoid live viral vaccines.

Other non-TNF biologic DMARDs are available. These include rituximab (most often used in combination with MTX), anakinra, abatacept, tofacitinib, baricitinib, and tocilizumab. Recent guidelines have been published to guide changes in medication doses, combinations, and switching agents [11] (Table 2).

Surgery

Surgery can provide pain relief, correct deformities, and improve function. Joint fusions, joint replacement, myofascial release, and other techniques are based on patient age, joint(s) involved, functional disability, and disease stage. Patients with cervical spine instability and refractory pain or neurological compromise are candidates for surgical intervention as well.

Clinical Course and Disease Activity

2011 ACR/EULAR guidelines provide separate definitions of remission of RA for use in clinical trials and clinical practice [12]. Disease activity can be measured in clinical practice with a Boolean-based method or with the Simplified Disease Activity Index (SDAI). Remission with the Boolean-based method requires patients to meet all of the following: (a) tender joint count $\leq$1; (b) swollen joint count $\leq$1; (c) CRP $\leq$1 mg/dL; and (d) patient global assessment $\leq$1 (based on a 0–10 scale survey). Remission categorized by SDAI requires patients to have a score of $\leq$3.3 which includes the following: simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and low CRP levels. To assess progression, patients are generally categorized into four stages: I (early RA), II (moderate progression), III (severe progression), and IV (terminal progression). Similar scales are available to quantify patients' functional capacity: Class I, able to perform activities of daily living; Class II, able to perform self-care and vocational activities, limited in other activities; Class III, able to perform self-care but limited in vocational activities; and Class IV, limited in ability to perform self-care. Using established scales and scoring criteria allows for clear communication between patients and multiple members of the healthcare team to determine the best treatment strategies for each individual patient.

Differentiating Rheumatoid Arthritis from Osteoarthritis

RA and OA are both relatively common clinical conditions. Since the treatment is different, early recognition and differentiation of the two conditions are clinically important. Patients with RA typically complain of morning stiffness, whereas the pain associated with OA increases through the

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Table 2 Indications for initiating and switching DMARDs [11]

Disease activity	Recommendation
Early RA (<6 months)	Provide DMARD combination therapy in patients with moderate or high disease activity and poor prognostic features (functional limitation, extra-articular disease, positive RF or anti-CCP antibodies, bony erosions on X-ray) Use anti-TNF agent MTX in those with high disease activity and poor prognostic features – except for infliximab, which is used in combination with MTX only (i.e., do not use infliximab as monotherapy)
Established RA if prognosis is not mentioned, use or switch to a nonbiologic or biologic DMARD regardless of prognostic features	Initiating and switching among nonbiologic DMARDs In patients who deteriorate after 3 months of DMARD monotherapy from low to moderate/high disease activity, add MTX, hydroxychloroquine, or leflunomide if no poor prognostic features For patients with persistent moderate/high disease activity after 3 months of MTX or MTX-DMARD combination therapy, add or switch to a different non-MTX DMARD
	Switching from nonbiologic to biologic DMARDs In patients with persistent moderate/high disease activity after 3 months of MTX monotherapy or MTX-DMARD combination therapy, add or switch to an anti-TNF biologic agent, abatacept, or rituximab In patients with persistent moderate/high disease activity after 3 months of intensified DMARD combination therapy or after a second DMARD, add or switch to an anti-TNF biologic agent
	Switching among biologic agents because of lack or loss of benefit In patients with persistent moderate/high disease activity not benefitting after 3 months of anti-TNF biologic therapy, switch to another anti-TNF biologic agent or a non-TNF biologic agent In patients with persistent moderate/high disease activity not benefitting after 6 months of non-TNF biologic therapy, switch to another non-TNF biologic agent or an anti-TNF biologic agent
	Switching biologic agents due to adverse effects In patients with high disease activity and serious event associated with anti-TNF biologic therapy, switch to a non-TNF biologic agent In patients with moderate or high disease activity after failure of non-TNF biologic therapy because of either a serious or a non-serious adverse event, switch to another non-TNF biologic agent or an anti-TNF biologic agent

ACR American College of Rheumatology, *CCP* cyclic citrullinated peptide, *DMARD* disease-modifying antirheumatic drug, *MTX* methotrexate, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *TNF* tumor necrosis factor

day and with use. The small joints of the hands and feet are symmetrically involved in RA and the distal interphalangeal joints rarely involved. OA often is less symmetric and typically impacts larger weight-bearing joints (hips, knees). However, distal and proximal interphalangeal joints of the hands are commonly symmetrically involved in OA. Soft tissue swelling and warmth are more common in RA. Plain films in RA show periarticular osteopenia and marginal erosions.

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OA patients often have bony osteophytes on physical examination or radiography. Laboratory findings in OA are normal, whereas RA shows elevations of ESR and CRP along with elevations in RF, anti-CCP, and characteristic CBC changes (anemia, thrombocytosis).

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) has a wide range of presentations in children. JIA was formerly known as juvenile rheumatoid arthritis (JRA) and is one of the most common chronic inflammatory diseases of childhood. The etiology is unknown, and multiple subtypes exist. Evidence suggests that antibiotic exposure in childhood potentially increases individual risk for JIA [13].

The diagnosis of JIA is based on history and physical examination. Arthritis must be present for at least 6 weeks before the diagnosis of JIA can be considered definitive. Onset occurs before the age of 16. The primary complaint is joint pain (which may manifest as a limp). Children often complain of pain less than adults, however, and in such cases, there is typically cessation of normal joint use such as refusing to stand in a toddler or infant. Onset can be either insidious or abrupt. Morning stiffness is common as is the "gelling phenomenon" (stiffness after periods of rest). An evanescent rash or psoriasis is the most common dermatologic findings. Physical examination is characterized by the presence of arthritis manifested by swelling, warmth, and erythema. Synovitis is common, and children will often hold joints in a position of maximal comfort (e.g., hip in flexion, abduction, and external rotation or knee in partial flexion). Range of motion is limited depending on the degree of pain and swelling. Complications resulting from any of the subtypes of JIA include joint contractures, muscular atrophy, uveitis, and leg length discrepancies.

Clinically, the International League of Associations for Rheumatology has subdivided JIA into multiple categories [14]. These categories include systemic-onset JIA, oligoarticular JIA, polyarticular JIA, psoriatic arthritis, enthesitis-related JIA, and undifferentiated arthritis. In systemic-onset JIA, children appear systemically ill and often complain of myalgias and arthralgias. An evanescent rash of the trunk and extremities is common. Organomegaly and lymphadenopathy may occur. Complaints of chest pain or shortness of breath should raise concern for serositis and a careful examination for rubs, rales, or gallop rhythms. Complications include hemolytic anemia, pericarditis, and (rarely) macrophage activation syndrome.

In oligoarticular JIA, fewer than four (and often only one) joints are involved. Oligoarticular JIA typically impacts weight-bearing joints (knees and ankles). Affected children do not look systemically ill and often walk without a limp despite obvious joint swelling. Anterior uveitis is present in up to 20% of children with oligoarticular (and polyarticular arthritis), and slit-lamp screening is important in these subtypes to exclude ocular disease [14]. Children with polyarticular JIA have five or more joints affected. Small and large joints can be affected, and rheumatoid nodules can be seen in active disease. Children with rheumatoid nodules generally are positive for rheumatoid factor.

Psoriatic arthritis in children is typically milder in children than in adults. It is monoarticular and involves the distal interphalangeal joints in 50% of cases. Nail pitting is present in over two-thirds of cases. Enthesis-related arthritis involves inflammation of the insertion of tendons and ligaments into bone. Pain and tenderness of periarticular structures are common. Additional diagnostic criteria include sacroiliac tenderness, positive HLA-B27 antigen screening, male gender, age over 6 years, the presence of anterior uveitis, and a first-degree relative with related spondyloarthropathies. Rare complications of enthesitis-related JIA additionally include restrictive lung disease and aortic insufficiency. Children with undifferentiated arthritis often have manifestations in multiple JIA categories.

The diagnosis of JIA is clinical. There are no diagnostic laboratory studies. Laboratories are helpful to rule out other disorders, help classify the type of arthritis, and determine the presence of

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any extra-articular manifestations of disease. Laboratory markers are also used to follow renal or hepatic function in children on various JIA treatment regimens.

The goal of treatment in patients with JIA is to control pain, maximize function, and minimize disability [15]. Current treatment regimens are available based on the following criteria:

(a) history of arthritis in four joints, (b) arthritis in five joints, (c) active sacroiliac arthritis, (d) systemic arthritis (inactive), and (e) systemic arthritis (active). The first group (four joints) generally includes patients with psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. In this group, nonsteroidal anti-inflammatory drugs (NSAIDs) are often useful for monoarticular disease. Intra-articular steroids and methotrexate are the next-line agents followed by treatment with TNF-α inhibitors. For patients with disease in five joints (RF-negative/RF-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis), NSAIDs have less of a role. Methotrexate and intra-articular steroids are used more commonly. Leflunomide and IL-6 inhibitors (tocilizumab) are alternatives to methotrexate. TNF-α inhibitors are next-line therapy as is abatacept or rituximab. Patients with active sacroiliac arthritis frequently respond to TNF-α inhibitors if they fail to respond to NSAIDs and/or methotrexate.

Patients with active systemic arthritis are treated with corticosteroids after a brief (2-week) NSAID trial. For patients with systemic JIA, anakinra is effective. Tocilizumab has recently been approved for use in systemic JIA as well. Patients who have active arthritis, but no signs of active systemic disease, are treated with NSAIDs, intra-articular injections, and methotrexate. Anakinra or TNF-α is typically used as second-line therapy.

Successful management of children with JIA is best served with an interprofessional and multidisciplinary approach. In addition to rheumatology, patients often benefit from consultation with physical therapy, occupational therapy, behavioral health, and social services to help manage this complex disease.

Reactive Arthritis (Reiter's Syndrome)

Reactive arthritis (formerly known as Reiter's syndrome) is an autoimmune response to infection associated with multiple gastrointestinal (GI) and genitourinary (GU) species [16]. *Shigella* sp., *Salmonella*, *Campylobacter*, and *Chlamydia trachomatis* have been most commonly implicated, but many others have also been associated with this syndrome. Clinically, reactive arthritis typically presents with uveitis/conjunctivitis ("can't see"), noninfectious urethritis ("can't pee"), and arthritis ("can't bend my knee").

Other symptoms include malaise, fatigue, and fever. Physical findings include an asymmetric oligoarthritis that typically involves the weight-bearing joints of the lower extremity and the fingers or toes, so-called sausage digits. While conjunctivitis is the most common eye disease associated with Reiter's syndrome, more worrisome eye diseases such as scleritis, uveitis, episcleritis, and corneal ulceration may be found on ocular exam. Urethral discharge, vulvovaginitis, balanitis circinata, and cervicitis are common genitourinary findings. Although uncommon, keratoderma blennorragicum, a psoriasiform rash, may be seen on the palms and soles. Other skin and nail findings include erythema nodosum and onychodystrophy.

Reactive arthritis typically follows 2–4 weeks after an antecedent GU/GI infection. Reactive arthritis is most common in young men [17]. The frequency of reactive arthritis relates to population rates of HLA-B27. The diagnosis of reactive arthritis is based on history and physical examination. There are no specific laboratory tests. CBC, ESR, CRP, HLA-B27, HIV, tuberculin skin testing, urinalysis, and serologies/cultures (particularly for sexually transmitted infections) can rule out associated disease. There is no curative therapy for reactive arthritis. Treatment is symptomatic or targeted toward the underlying disease [18]. While NSAIDs are frequently used as initial therapy, sulfasalazine, methotrexate, and anti-TNF agents are useful second-line agents for patients with persistent symptoms and no relief from NSAIDs. Any underlying disease that is identified should be treated accordingly.

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Systemic Lupus Erythematosus

Background and Pathophysiology

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder affecting multiple organ systems. SLE can impact any organ system but most commonly involves the skin, musculoskeletal system, renal system, cardiovascular system, hematopoietic system, and nervous system. While the exact cause is unknown, SLE is an autoimmune disorder that is characterized by autoantibody formation and inflammation. T cells have traditionally been implicated as playing a central role in SLE pathogenesis, but other inflammatory cells clearly are implicated. Circulating immune complexes interact with native tissues and activate complement and the inflammatory cascade. Genetic defects in lymphocyte signaling, apoptosis, and the clearance of immune complexes have been identified. Interferon regulatory factor 5 (IRF-5) genetic polymorphisms associated with SLE have been identified in different ethnic populations.

The annual incidence of SLE is roughly 5 cases per 100,000 individuals. Higher rates of SLE are reported in blacks and Hispanics. Most cases (90%) occur in women, particularly after reaching childbearing age. Male cases are described in individuals with Klinefelter syndrome (XXY), suggesting a hormonal contribution to the pathogenesis of SLE. Survival rates for SLE patients have improved markedly over the past several decades. Ten-year survival rates currently exceed 90%.

Clinical Presentation

One of the characteristic manifestations of SLE is a malar rash that spares the nasolabial folds. Other common features include other mucocutaneous abnormalities, joint pain, fever, neurological events (seizures or stroke), proteinuria/cellular casts in urine sediment/renal insufficiency, lymphadenopathy, sicca symptoms, and pleuritis. Abnormalities in hematologic indices are common as well. Clinically, the mnemonic "SOAP BRAIN MD" has been applied to the 11 ACR classification criteria for SLE (Table 3): S (serositis) O (oral ulcers) A (arthritis) P (photosensitivity) B (blood disorders) R (renal involvement) A (antinuclear antibodies) I (immunologic data dsDNA) N (neurologic findings) M (malar rash) D (discoid rash). EULAR has further defined SLE to require elevated ANA levels as an entry point for disease identification. After ANA levels are confirmed, then the diagnosis is based on a weighted score system which includes constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal, and immunology domains. The updated criteria have a sensitivity of 96.1% and a specificity of 93.4% for the diagnosis of SLE [19].

Fever, fatigue, and weight loss are the most common constitutional complaints in patients with SLE (new-onset or with flare of active disease). Joint pain is the most common musculoskeletal complaint, followed by myalgias and arthritis. The arthritis is typically symmetrical, and pain may be out of proportion to the degree of joint swelling. Avascular necrosis is more common in patients with SLE, especially those taking corticosteroids. Malar rash, discoid rash, and photosensitivity are the most common cutaneous features. Other associated cutaneous findings include Raynaud's phenomenon, telangiectasia, livedo reticularis, alopecia, discoid lesions, and urticarial.

CNS involvement is common in SLE. The most common are seizures, stroke, and mental status changes (psychosis). The ACR has developed case definitions for multiple neuropsychiatric syndromes associated with SLE including delirium, psychosis, or seizures [20]. Pulmonary findings associated with SLE include pleurisy, pneumonitis, interstitial lung disease, pulmonary hypertension, and an exudative pleural effusion. Corresponding physical findings would include pulmonary rubs, rales, and dullness to percussion. Complaints of chest pain in patients with SLE should not be ignored. Pericarditis is the most common cardiovascular complication of SLE. Patients with pericarditis typically complain of chest pain that is relieved by leaning forward. Pulmonary hypertension can present with progressive dyspnea.

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Table 3 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for systemic lupus erythematosus (SLE) [19]

Entry criteria			
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test			
Additive criteria			
Clinical domain and criteria	**Weight**	**Clinical domain and criteria**	**Weight**
Constitutional		**Renal**	
Fever	2	Proteinuria >0.5 g/24 h	4
Hematologic		Renal biopsy class II or V lupus nephritis	8
Leukopenia	3	Renal biopsy class III or IV lupus nephritis	10
Thrombocytopenia	4	**Serosal**	
Autoimmune hemolysis	4	Pleural or pericardial effusion	5
Neuropsychiatric		Acute pericarditis	6
Delirium	2	**Immunology domain and criteria**	**Weight**
Psychosis	3	**Antiphospholipid antibodies**	
Seizure	5	Anti-cardiolipin antibodies OR	
Mucocutaneous		Anti-β_2GP1 antibodies OR	
Non-scarring alopecia	2	Lupus anticoagulant	2
Oral ulcers	2	**Complement proteins**	
Subacute cutaneous OR discoid lupus	4	Low C3 OR low C4	3
Acute cutaneous lupus	6	Low C3 AND low C4	4
Musculoskeletal		**SLE-specific antibodies**	
Join involvement	6	Anti-dsDNA antibody∗ OR	
		Anti-Smith antibody	6

To classify systemic lupus erythematous (SLE), patients must first meet the entry criteria of elevated ANA titer. Additive criteria are then added but only the highest weighted criterion per domain is counted toward the total score. SLE classification requires at least one clinical criterion and ≥ 10 points. Occurrence of a criterion on at least one occasion is sufficient to be counted. Criteria do not need to occur simultaneously
Anti-β_2GP1 anti- β_2-glycoprotein 1, *anti-dsDNA* anti-double-stranded DNA

Laboratory Findings

Patients with suspected SLE should have a complete blood count (with differential), basic metabolic profile (creatinine and glomerular filtration rate), and formal urinalysis (microscopy). The CBC may reveal leukopenia, anemia, lymphopenia, and/or thrombocytopenia. Abnormalities in urine sediment may include proteinuria or casts. The metabolic profile examines renal function (changes in glomerular filtration rate), looking for signs of lupus nephritis. Erythrocyte sedimentation rates and C-reactive protein levels are often elevated in SLE. Complement protein levels (C3, C4, and CH50) are commonly depressed consumption in active lupus nephritis.

There are multiple autoantibody tests available to aid in the diagnosis of SLE. Antinuclear antibody (ANA) testing is 95% sensitive for SLE but is not specific. However, based on EULAR/ACR criteria, the diagnosis of SLE requires a positive ANA test or equivalent (Table 3). Anti-dsDNA is highly specific but has a lower sensitivity. Levels vary with disease activity. Anti-Sm is the most specific antibody test for SLE but has a very low sensitivity.

Anti-cardiolipin antibodies, anti-β2GP1 antibodies, and lupus anticoagulant testing are laboratory tests that can identify antiphospholipid antibodies that may be associated with the antiphospholipid antibody syndrome. All patients with a diagnosis of SLE should be tested for concurrent antiphospholipid antibody syndrome.

Treatment

The updated European League Against Rheumatism (EULAR) recommendations provide sound guidance for the treatment of SLE [21]. For

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patients who do not have major organ involvement, corticosteroids and antimalarials are helpful. Traditionally, hydroxychloroquine has been the cornerstone therapy for SLE to prevent flares and reduce disease mortality. NSAIDs can be used for short periods as well if there is not risk of exacerbating underlying organ disorder, particularly renal disease. For cases refractory to steroids and antimalarials, immunosuppressive agents such as azathioprine, methotrexate, and mycophenolate are also useful for certain manifestations and control of systemic disease. Cyclophosphamide can be used in severe life-threatening situations for patients not responding to immunosuppressive therapy. The monoclonal antibody belimumab can be used in patients with frequent relapses. Rituximab should be reserved for organ-threatening disease. Additional guidelines for the management of lupus nephritis were published by the ACR in 2012 [22].

As with many of the rheumatic diseases, an interprofessional, multidisciplinary team is helpful to maximize clinical outcomes for patients with SLE. Consultations with multiple specialties including rheumatology, neurology, nephrology, pulmonology, cardiology, dermatology, hematology, and maternal fetal medicine may be necessary. Patient education is also important. Patients should avoid any known triggers for SLE flares. Patients should wear sunscreen and minimize ultraviolet light exposure to reduce photosensitivity reactions. Patients with SLE often require vitamin D supplementation. Exercise is important to maximize functional capacity, avoid muscular atrophy, and maximize bone mineralization. Patients with SLE should not smoke or use tobacco products.

Raynaud's Disease (Primary Raynaud's Phenomenon)

Primary Raynaud's phenomenon, or Raynaud's disease, is a reactive vasospasm of the fingers and toes typically in response to stress or cold exposure. Primary Raynaud's phenomenon is not associated with any other systemic illness. Secondary Raynaud's phenomenon is associated with some other form of clinical illness typically autoimmune in nature with scleroderma, SLE, and mixed-connective tissue disorder being the most common. The cause of Raynaud's disease remains unknown. The disease is slightly more common in women and has no racial predilection unless it is associated with an autoimmune disorder. It most commonly occurs in the second and third decades of life. Raynaud's disease is characterized clinically by pallor (white), followed by cyanosis (blue), and erythema (red) on rewarming. The fingers are most commonly affected followed by the toes and ears [24].

When evaluating patients for Raynaud's disease, a careful history is important. This should particularly include a prior history of frostbite and prior repetitive use of vibrating tools, which predispose to vasospasm. Occupational exposures to organic solvents have also been associated with Raynaud's disease. Secondary Raynaud's phenomenon has been associated with autoimmune diseases (scleroderma, SLE), infectious syndromes (hepatitis B and C), neoplastic syndromes (leukemia, lymphoma), environmental exposures, medications (beta-blockers, methylphenidate, oral contraceptives), and hematologic (polycythemia) and metabolic syndromes (diabetes, pheochromocytoma). Historically, the color demarcation between affected and unaffected areas of skin is remarkable. The digits should be examined for sclerodactyly, ulceration, and capillary blush. Nail fold microscopy can reveal abnormalities in capillary loops. Immersing the patient's affected extremity in ice water can often reproduce the symptoms but is typically not necessary for diagnosis. Laboratory testing is helpful in ruling out potential causes of secondary Raynaud's phenomenon, in particular antinuclear antibodies. Diagnostic criteria for primary Raynaud's phenomenon have been established [23] and include trigger by exposure to cold/stress, bilateral (symmetric) involvement, no necrosis, no underlying systemic cause, normal capillary findings on microscopy, and no laboratory evidence of inflammation or antinuclear factors.

The mainstay of treatment for Raynaud's disease centers on patient education and lifestyle

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change. Patients should be instructed to wear warm socks, gloves, or mittens and avoid unnecessary cold exposure. Tobacco cessation is important (nicotine is a potent vasoconstrictor). If conservative strategies fail, calcium channel blockers are the traditional pharmacological treatment [23]. Nifedipine (30–120 mg of extended release) is typically the agent of choice. Topical nitroglycerin (1%) and the prostaglandin analogue (iloprost) have shown promise in limited numbers of studies, but extended use data is lacking.

Systemic Sclerosis

Systemic sclerosis (SSc; scleroderma) is a systemic autoimmune disorder, which results in abnormal collagen deposition in the skin and internal organs resulting in progressive fibrosis of the skin, lungs, heart, gastrointestinal tract, and kidneys. Systemic sclerosis represents a broad spectrum of disease with multiple clinical forms. CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) is a form of scleroderma characterized by cutaneous systemic sclerosis typically involving regions distal to the elbows and knees. Diffuse cutaneous systemic sclerosis is more severe and often involves the internal organs to some degree. Diffuse systemic sclerosis has a more fulminant course with organ involvement and rapid progression. The ACR/EULAR criteria for classification of systemic sclerosis were revised in 2013 [24] (Table 4).

Three important processes are involved in the pathophysiology of SSc: (1) alterations in cellular and humoral immunity, (2) excessive collagen deposition, and (3) fibroproliferative disease of small arteries/arterioles. The resulting vasculopathy and tissue fibrosis result in organ dysfunction and clinical disease. While the exact etiology is not known, exposure to silica, solvents, and/or radiation in genetically susceptible individuals has all been hypothesized to trigger the disease [25]. Viruses (herpesvirus, cytomegalovirus, parvovirus) have also been proposed to accelerate the disease in genetically susceptible individuals. SSc is more common in women. There appears to be a higher incidence rate in blacks as compared to whites. In the United States, the highest

Table 4 ACR/EULAR revised systemic sclerosis classification criteria [24]

Item	Sub-item(s)	Score[a]
Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints (presence of this criterion is sufficient criterion for SSc classification)	None	9
Skin thickening of the fingers (count the higher score only)	Puffy fingers	2
	Sclerodactyly (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (count the higher score only)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	None	2
Abnormal nail fold capillaries	None	2
Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	None	3
Systemic sclerosis-related autoantibodies (maximum score is 3)	Anti-centromere	3
	Anti-topoisomerase I	3
	Anti-RNA polymerase III	3

[a]The total score is determined by adding the maximum score in each category. Patients with a total score equal to or greater than 9 are classified as having definite systemic sclerosis

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prevalence of SSc is in the Choctaw Indian tribe. The peak incidence is 30–50 years of age.

Patients with SSc present with signs and symptoms involving many different organ systems. Skin complaints include tightness and induration (edema), sclerodactyly, pruritus, and pigmentary change. Vascular phenomena typically present as secondary Raynaud's phenomenon. Telangiectasias are also common. Gastrointestinal complaints include reflux, dyspepsia, and altered bowel habits (constipation, diarrhea, incontinence). Respiratory manifestations include dyspnea and cough. Musculoskeletal complaints include myalgias, arthralgias, weakness, and decreased joint range of motion. Common physical findings include sclerodactyly, microstomia, telangiectasia, rales, and an accentuated P2 (pulmonary hypertension).

The diagnosis of SSc is based on history and physical examination. Baseline laboratory studies (CBC, CPK, ESR, B-NP, autoantibody profiles) can help exclude other causes and follow disease progression. Endoscopy, echocardiography, and pulmonary function tests can provide further insight to track target organ function.

There is no cure for scleroderma. Treatment is designed to optimize function of involved organ systems, prevent complications, and provide symptomatic relief. Patients should routinely be encouraged to stop smoking [26]. Investigational therapies are under way to treat skin fibrosis. Pruritus is best managed with moisturizers and antihistamines. Raynaud's phenomenon can be managed with lifestyle changes and calcium channel blockers. Treatment of pulmonary hypertension includes either bosentan, ambrisentan, or sildenafil [25]. Severe SSc-related pulmonary hypertension can be treated with epoprostenol infusions. Antacids, histamine blockers (H2), and proton pump inhibitors can treat common reflux symptoms associated with SSc. Cyclophosphamide is used to treat pulmonary fibrosis in patients with SSc, and nintedanib can be used to slow the rate of pulmonary function decline.

As with other conditions, the broad spectrum of SSc may require input and guidance from a range of consultants. Coordinating care and communication in patients with extensive disease can be a challenge. Rheumatology, pulmonology, cardiology, gastroenterology, surgery, nephrology, physical therapy, occupational therapy, and other services may need to be involved. Developing a robust patient-centered team with clear lines of communication is important to reduce morbidity and improve outcomes.

Sjögren's Syndrome

Sjögren's syndrome is a chronic inflammatory autoimmune disorder. It involves lymphocytic infiltrates within exocrine organs and is characterized by the combination of keratoconjunctivitis sicca or xerophthalmia (dry eyes), xerostomia (dry mouth), and parotid enlargement. Extraglandular features include arthralgias, myalgias, arthritis, lymphadenopathy, neuropathy, and Raynaud's phenomenon. The EULAR/ACR classification for Sjögren's syndrome includes a weighted score based on five categories: (a) labial salivary gland with focal lymphocytic sialadenitis and focus score of $\geq$1 foci/4 mm^2 (3 points); (b) positive anti-SSA or anti-Ro antibodies (3 points); (c) ocular staining score $\geq$ 5 (or van Bijsterveld score $\geq$ 4) in at least one eye (1 point); (d) Schirmer's test $\leq$5 mm/5 min in at least one eye (1 point); and (e) unstimulated whole saliva flow rate $\leq$ 0.1 mL/min (1 point). If a patient has four or more points and does not have an excluding criteria (i.e., history of head or neck radiation, active hepatitis C infection, AIDS, sarcoidosis, amyloidosis, graft versus host disease, IgG4-related disease), then they meet the criteria for Sjögren's syndrome diagnosis [27].

Sjögren's syndrome is more common in patients with HLA-DR52 and affects women nine times more often than men [28]. Sjögren's syndrome is more common in older adults, with an average age of onset in the fourth and fifth decade of life. It is hypothesized that Sjögren's syndrome is triggered by viral disease, though proof remains inconclusive. Many medications (antidepressants, antihistamines, anticholinergics, diuretics, beta-blockers) can also cause xerostomia but should not be confused with Sjögren's syndrome. Outside of sicca symptoms

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(dry eyes and dry mouth), patients most commonly present with parotitis and cutaneous complaints such as dry skin and pruritis. Dryness of the aerodigestive tract can result in a chronic cough, dysphagia, and a globus sensation. Common physical findings relate to ocular and oral dryness. Angular cheilitis; dental caries; a dry, erythematous, smooth tongue; and chapped lips are common. Parotid gland enlargement occurs in 20–60% of Sjögren's syndrome patients.

The diagnosis of Sjögren's syndrome is based on clinical history (sicca symptoms) and physical examination. Laboratory testing to quantify salivary (sialometry) and lacrimal (Schirmer's test) function is supportive of the diagnosis. Autoantibodies are common in Sjögren's syndrome with anti-SSA and anti-SSB being the most common. Treatment options for Sjögren's syndrome patients are limited and primarily focus on symptom relief. Liberal use of ocular lubricants, skin lubricants, and vaginal lubricants can help mitigate dryness. Humidifiers and frequent sips of water can help alleviate dry mouth. Pilocarpine, artificial saliva, and cevimeline have been used for more severe cases of xerostomia [29]. If major organs are involved, the use of immunosuppressive therapy (cyclophosphamide), rituximab, or systemic corticosteroids is appropriate. Such cases are best managed in the context of a multidisciplinary team including rheumatology, pulmonology, and nephrology depending on the extent of extraglandular disease. Sjögren's syndrome patients should have appropriate eye health and oral health professionals as part of this team.

Polymyalgia Rheumatica (PMR)

Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder that typically affects individuals over the age of 50. The cause of PMR is not known. The pathology of PMR is similar to giant cell arteritis or temporal arteritis. The disease appears to be polygenic in origin, perhaps triggered by an environmental factor (likely a virus) that results in cytokine production due to macrophage and T-cell activation. Polymyalgia rheumatica has an annual incidence of approximately 53 cases per 100,000 persons over age 50 annually in the United States. PMR is more common in white patients (rare in blacks) and more common in women [30]. The median age at the time of diagnosis is 72 years. One in three patients with polymyalgia rheumatica also has temporal arteritis.

The predominant clinical features of PMR are pain or weakness of the hips, shoulders, and neck that are usually associated with morning stiffness. Patients may also complain of constitutional symptoms including fatigue, weight loss, and low-grade fever. In 2012, EULAR/ACR published scoring criteria for patients with PMR: (a) morning stiffness >45 min (2 points), (b) hip pain and limited ROM (1 point), (c) rheumatoid factor (RF) and anticitrullinated protein antibody (CCP) negative (2 points), and (d) no peripheral joint pain (1 point) [31]. Patients with four or more points are likely to have PMR (compared to other spondyloarthropathies or inflammatory arthritides). On physical examination, patients may have a low-grade temperature. They often appear fatigued. Patients have normal muscle strength and no atrophy. There is tenderness to palpation, particularly of the hip and shoulder girdles, but many investigators feel that this is due to synovitis. ROM is often reduced due to the pain. Imaging is not routinely used for diagnosis. The erythrocyte sedimentation rate is the most sensitive (but not specific) laboratory test for PMR. ESR is almost always >40 mm/h and characteristically exceeds 100 mm/h. Creatine phosphokinase levels are normal as are ANA, complement, RF, and anti-CCP levels.

Corticosteroids are generally the cornerstone of treatment for patients with PMR. Patients generally respond well to a prednisone dose of 12.5 to 25 mg/day. If a patient does not respond quickly (within 2–4 weeks) to corticosteroids, other diagnoses should be considered. Patients often require steroids for a prolonged period (1–2 years). Patients on chronic steroid therapy should receive calcium and vitamin D supplementation and regular DEXA scans to assess bone health [32]. When attempts are made to wean a patient off prednisone, the dose is decreased by only 1 mg/month. Methotrexate and TNF-α inhibitors

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have also been used as steroid-sparing treatments for PMR.

Giant Cell Arteritis (Temporal Arteritis)

Giant cell arteritis (GCA; temporal arteritis) is a cell-mediated inflammatory systemic vasculitis. GCA is the most common systemic vasculitis in adults. Pathophysiology of GCA is characterized by inflammation of the vascular wall of affected arteries (e.g., the temporal artery) which results in endothelial injury, luminal narrowing, and distal ischemia. Like polymyalgia rheumatica, GCA typically presents in patients over 50 years of age [33]. The disease incidence peaks in the eighth decade of life. GCA is more common in women (3:1) and in whites of Northern European descent.

The onset of GCA is variable. Some patients have an insidious onset, while for others it is abrupt. Often there is a constitutional prodrome with patients complaining of anorexia, malaise, myalgias, night sweats, and weight loss in the preceding days to weeks. Headache is the most common symptom associated with GCA (present in three quarters of patients) [34]. The headache is most commonly temporal-occipital in location and described as "throbbing" and "continuous." Many patients are tender to palpation over the temporal artery. Jaw claudication and shoulder and/or hip/pelvic girdle pain are often present as well (as in PMR). Some patients with GCA report visual symptoms. Symptoms are often transient, but sudden loss of vision is a poor sign and can be permanent without immediate treatment. The most common visual symptoms included blurring, visual loss, diplopia, hemianopia, or amaurosis fugax.

Patients with GCA (as in PMR) typically have an elevated ESR (50 mm/h to over 100 mm/h). Definitive diagnosis requires a temporal artery biopsy (TAB). Treatment should not be withheld pending biopsy results, and specimens are more likely to be positive if obtained within 24 h of beginning treatment. Recently, the use of color duplex ultrasonography has shown promise as a diagnostic complement to TAB. High-resolution MRI has been used for a similar purpose. The ACR [35] and others [36] have developed diagnostic criteria for GCA including (a) age over 50, (b) new-onset localized headache, (c) temporal artery tenderness to palpation (or decreased pulsation), (d) ESR 50 mm/h, and (e) positive TAB (vasculitis with mononuclear infiltration). High-dose corticosteroid therapy is the cornerstone of therapy for GCA [37]. Patients with visual symptoms have a markedly increased chance of visual improvement if steroid therapy is initiated within 24 h. Oral prednisone (40–60 mg/day; some sources suggest 80–100 mg/day in patients with visual or neurological symptoms consistent with GCA) should be started immediately while arranging for TAB. Intravenous methylprednisolone (250–1000 mg/day for 3 days) is an alternative to oral prednisone. Once symptoms have improved, steroids should be tapered to the lowest dose necessary to suppress symptoms. Patients often require prolonged treatment with corticosteroids. Symptoms and measurement of acute phase reactants serve as a guide to tapering the dose of corticosteroids. Methotrexate, tocilizumab (an interleukin-6 receptor monoclonal antibody), and TNF-α antagonists have been used as steroid-sparing agents in patients requiring higher doses of prednisone (5–10 mg/day) for prolonged periods of time. GCA is best managed in consultation with a rheumatologist in the context of high-dose steroids and surgery consultation required to assist with TAB. Ophthalmology consultation in the context of visual changes should be entertained if the diagnosis is uncertain.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic inflammatory seronegative spondyloarthropathy primarily involving the spine (sacroiliac joint and axial skeleton). The disease is more common in men (3:1) and typically presents during adulthood. More than half of the patients with ankylosing spondylitis present complaining of low-back pain. Features distinguishing AS from mechanical low-back pain include morning stiffness, pain that is unrelieved with rest, and pain that awakens

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patients from sleep [38]. The pain associated with AS often radiates to the buttocks but rarely below the knee (as seen with sciatica). The onset of pain is often insidious and tends to improve with exercise. Fatigue is reported in 65% of patients. Extra-articular manifestations of AS include uveitis, pulmonary, cardiovascular, renal, gastrointestinal, and metabolic bone diseases. Patients may also have peripheral joint involvement (large joints are more commonly involved than small joints) or complain of other sites of enthesopathic pain (e.g., Achilles tendon, plantar fascia) [38, 39]. Onset after the age of 40 is unusual. Over 90% of Caucasian patients with AS are HLA-B27 positive. However, only 1–2% of patients who are positive for HLA-B27 develop ankylosing spondylitis, suggesting a role of other factors in the onset of disease [40].

Early diagnosis of AS is important to maximize functional outcomes. The diagnosis of AS is based on a combination of clinical and radiographic findings [41, 42] (Table 5). The insidious onset of low-back pain that is worse in the morning, relieved with activity, lasting for more than 3 months in patients under the age of 40 should raise the suspicion for AS [43].

Physical examination should include documentation of lumbar range of motion in particular. The two most commonly used tests to assess spinal flexion are Schober's test and Moll's flexion test. Schober's test is performed with the patient standing. Identify the top of the sacrum, and mark a spot on the spine 10 cm above and 5 cm below. In normal individuals, this distance increases by at least 5 cm with forward flexion. The Moll's lateral flexion test is performed by marking a point 20 cm above the iliac crest at the midaxillary line. This distance increases by at least 3 cm with lateral flexion in normal individuals. Uveitis (typically unilateral) is the most common extra-articular manifestation of AS [44], but the cardiopulmonary, renal, gastrointestinal, and neurovascular systems can all be involved.

Radiographic studies help to confirm the diagnosis of AS [45]. Involvement of the sacroiliac joint is required to diagnose AS. Radiographic signs of AS include vertebral "squaring" (erosions of the margins of the vertebral bodies) and sclerosis of the vertebral margins (Romanus lesion). Sacroiliac disease is usually bilateral in AS. If the disease has progressed, patients develop a characteristic "bamboo spine" appearance on X-ray. Power Doppler ultrasonography, MRI, and CT also reveal characteristic signs of sacroiliitis. The ESR is elevated. It is easy to measure the flexibility of the spine, which is decreased in most patients.

The goals of treatment of ankylosing spondylitis are to decrease pain and maintain functional status [46]. No specific disease-modifying treatment currently exists for patients with AS. NSAIDs are the initial drugs of choice to control inflammation and decrease pain. Sulfasalazine is helpful in patients who are

Table 5 New York and Rome criteria for diagnosis of ankylosing spondylitis [33, 34]

New York criteria	Rome criteria
Low-back pain with inflammatory characteristics Limitation of lumbar spine motion in sagittal and frontal planes Decreased chest expansion Bilateral sacroiliitis grade 2 or higher∗ Unilateral sacroiliitis grade 3 or higher∗	Low-back pain and stiffness that is not relieved by rest for >3 months Thoracic pain and stiffness Limited motion in the lumbar spine Limited chest expansion History of uveitis
∗Diagnose ankylosing spondylitis if patient presents with any clinical criteria	Diagnosis ankylosing spondylitis when any clinical criteria present with bilateral sacroiliitis grade 2 or higher radiographic sacroiliac (SI) grades Grade 0 – Normal Grade 1 – Suspicious Grade 2 – Minimal sacroiliitis Grade 3 – Moderate sacroiliitis Grade 4 – Ankylosis

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unresponsive to NSAIDs. TNF-α antagonists are effective in the treatment of AS. Infliximab, adalimumab, golimumab, certolizumab pegol, and etanercept have all been approved by the FDA as therapy for AS when NSAID therapy has failed. Ixekizumab, an interleukin-17 inhibitor, can be considered as a second-line initial therapy or when NSAIDs and TNF-α antagonists have failed. Patients should be screened for hepatitis B, HIV, and latent tuberculosis before initiating TNF-α antagonist therapy. Complex cases are best managed in the context of a multidisciplinary team including rheumatology, pulmonology, ophthalmology, cardiology, physical therapy, and orthopedic surgery depending on the extent of disease [46, 47].

Psoriatic Arthritis

Psoriatic arthritis is a seronegative inflammatory arthritis that is variable and occurs in about 7–42% of patients with psoriasis (▶ Chap. 120, "Common Dermatoses"). Psoriasis typically precedes the appearance of arthritis by several years. The onset is typically insidious with patients primarily complaining of stiffness and pain. Psoriatic arthritis is also associated with enthesopathy (inflammation at the insertion of ligament/tendon into bone). The Achilles tendon and plantar fascia are commonly involved. One-third of patients will exhibit dactylitis or sausage digit. Skin findings are consistent with psoriasis and include scaly erythematous plaques, guttate lesions, and erythroderma. Psoriatic nail changes (pitting, hyperkeratosis, Beau's lines, transverse ridging) are common. With the exception of skin disease, extra-articular findings are less common in psoriatic arthritis patients than in other inflammatory arthritides. Guidelines for diagnosis [48] include the Classification Criteria for Psoriatic Arthritis (CASPAR) scoring system (3 points total from the following):

- Active psoriasis (2 points)
- History of psoriasis – no active psoriasis (1 point)
- Family history of psoriasis – no active psoriasis (1 point)
- Dactylitis (1 point)
- Juxta-articular new bone formation (1 point)
- Serum RF negative (1 point)
- Nail dystrophy (1 point)

There are no diagnostic laboratory tests for psoriatic arthritis. ESR and CRP are often elevated. X-rays often show joint space narrowing of the interphalangeal joints with periostitis and may show the characteristic "pencil-in-cup" deformity. NSAIDs are the initial treatment of choice, and several DMARDs have been approved for the treatment of psoriatic arthritis including methotrexate, sulfasalazine, cyclosporine, leflunomide, and TNF-α antagonists [49]. If patients have an inadequate response to nonbiologic DMARDs, biologic therapy can be helpful. Biologic options include TNF-α antagonists (adalimumab, certolizumab, etanercept, golimumab, infliximab), interleukin-17 inhibitors (ixekizumab, secukinumab), interleukin-12/23 inhibitors (ustekinumab), CD80/86 receptor antagonists (abatacept), and Janus kinase inhibitors (tofacitinib). Apremilast (a phosphodiesterase-4 inhibitor) is a nonbiologic approved by the FDA for treatment of psoriatic arthritis in adults.

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Selected Disorders of the Musculoskeletal System

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Patrick Anderl

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Fibromyalgia

General Principles

Definition/Background

Fibromyalgia is a chronic, idiopathic, non-articular disorder of pain regulation. Its etiology is unknown, and pathophysiology is uncertain [1]. Though initially called fibrositis, there is no evidence of inflammation in any of the affected tissues [2]. There are no diagnostic laboratory tests for fibromyalgia. Diagnosis is symptom based and often requires a clinician familiar with these chronic widespread pain conditions for confirmation of the diagnosis [3].

Like many other chronic pain syndromes, fibromyalgia can be a controversial diagnosis and at times has been considered psychogenic or psychosomatic. More recently, however, it has been classified as a form of central nervous system sensitization [4].

Epidemiology

Fibromyalgia is the most common cause of chronic widespread musculoskeletal pain [1, 2]. It has been observed in all ages and is more common in women than in men. Prevalence increases with age and peaks between 60 and 79 years, where it is estimated to affect >7% of women [5]. Prevalence in the general population is estimated to be between 1% and 6% depending based on which diagnostic criteria is used, but overall fibromyalgia is likely under recognized in clinical practice [6].

Diagnosis

Fibromyalgia should be suspected in anyone complaining of pain of at least 3 months duration. Several classification criteria have been proposed,

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but the gold standard continues to be symptom based diagnosis [3]. There are no confirmatory tests or biomarkers.

History

The cardinal symptoms of fibromyalgia are widespread musculoskeletal (also termed multisite) pain, fatigue, and sleep disturbances, but other cognitive, neurologic, and somatic complaints are common [7]. Most patients complain of myalgias, arthralgias, and swollen joints, though synovitis is not present on exam. Fatigue and unrefreshing sleep can be triggered by even minor physical activity, although prolonged inactivity also exacerbates symptoms. Cognitive disturbances, poor attention, and difficulty completing tasks are often described and referred to as "fibro fog" [8]. Depression and anxiety are common coexisting disorders [9]. Other somatic complaints include headache, paresthesias, nondescript abdominal or chest pain, IBS symptoms, pelvic pain, and bladder symptoms. Autonomic complaints include dry eye, Raynaud phenomenon, hypotension, and tachycardia. Patients may also complain of weather-related exacerbations and other environmental hypersensitivities.

Physical Examination

The usual findings include mild to severe tenderness on palpation of various soft tissue sites. There should be no soft tissue or joint swelling or redness. Common tender points include, but are not limited to, the occiput, low cervical spine, trapezius, supraspinatus, second rib, lateral epicondyle, buttock, greater trochanter, and knee [10].

Neurologic testing may reveal subtle findings suggesting peripheral neuropathy or minor sensory and motor abnormalities [11]. Fibromyalgia does not cause any focal neurological deficits. The remainder of physical exam and testing is usually unremarkable.

Classification

There have been several published classification criteria for fibromyalgia. Most were developed and used for clinical research and epidemiologic studies but have not been validated for patient diagnosis [3]. The older 1990 American College of Rheumatology (ACR) classification criteria have been used in most clinical and therapeutic trials.

A different classification system is used in clinical settings. In 2010 the Analgesic, Anesthetic, and Addiction Clinical Trial Translocations Innovations Opportunities and Networks (ACTTION) and American Pain Society (APS) formulated the ACTTION-APS pain taxonomy (AAPT) in order to help differentiate FM from other chronic pain disorders [12].

The 1990 ACR criteria requires symptoms of widespread pain occurring both above and below the waist affecting both sides of the body as well as identification of at least 11 of 18 specifically defined tender points [10]. The inability to standardize the tender point examination was the main impetus in moving away from these criteria.

The 2010 ACR preliminary diagnostic criteria uses a subjective symptom survey called the widespread pain index (WPI) and a symptom severity scale (SSS) rating to assist in diagnosis [13]. It does not require a tender point exam. See Table 1 for the WPI score criteria. See Table 2 for the SSS score criteria.

Fibromyalgia is diagnosed if all of the following are met:

- WPI $>$ 7 and SSS $>$ 5 OR WPI 3–6 and SSS $>$ 9
- Symptoms have been present for at least 3 months
- There is no other more likely alternative diagnosis

The AAPT diagnostic criteria listed in Table 3 are much more subjective and, as a result, easier to use clinically. Diagnosis requires multisite pain (MSP) and sleep problems or fatigue present for greater than 3 months.

Differential Diagnosis

Appropriate diagnosis of fibromyalgia requires the exclusion of other causative conditions. Alternative diagnoses to consider include systemic rheumatic diseases, myopathies, endocrinopathies, myofascial pain syndrome, and neurologic disorders. It is also

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Table 1 Widespread pain index score

Widespread pain index (final score will be 0–19)			
How many areas has the patient had pain in the last week?			
Shoulder girdle, left	Shoulder girdle, right	Hip, left (buttock or trochanter)	Hip, right (buttock or trochanter)
Upper arm, left	Upper arm, right	Lower arm, left	Lower arm, right
Upper leg, left	Upper leg, right	Lower leg, left	Lower leg, right
Jaw, left	Jaw, right	Neck	Chest
Upper back	Lower back	Abdomen	

Adapted from Wolfe et al. [13]

Table 2 Symptom severity scale score

Symptom severity scale score (final score will be 0–12)				
Indicate the level of severity of each symptom listed below over the last week, where: 0 = no problem 1 = slight of mild problems, mild or intermittent 2 = moderate, considerable problems, often present 3 = severe, pervasive, continuous				
Fatigue	0	1	2	3
Waking unrefreshed	0	1	2	3
Cognitive symptoms	0	1	2	3
Somatic symptoms[a]	0 None	1 Few	2 Moderate	3 Many
Final score will be 0–12				

Adapted from Wolfe et al. [13]

[a]Somatic symptoms can include muscle pain, irritable bowel syndrome, fatigue/tiredness, memory problem, muscle weakness, headache, abdominal cramping, numbness/tingling, dizziness, insomnia, depression, constipation, abdominal pain, nausea, nervousness, chest pain, blurry vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives, tinnitus, vomiting, heartburn, oral ulcer, change in taste, seizures, dry eye, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, bladder spasms

Table 3 AAPT diagnostic criteria

The following symptoms present for 3 or more months		
Pain in six or more of the following nine sites		
Head	Left arm	Right arm
Chest	Abdomen	Upper back
Lower back	Left leg	Right leg
Moderate to severe sleep problems OR fatigue		

Adapted from Arnold et al. [12]

helpful to consider overlapping disorders such as functional somatic syndromes, chronic fatigue syndrome, and psychiatric disorders.

Laboratory and Imaging

Lab studies should focus on ruling out other alternative diagnoses being considered. This often includes CBC, thyroid function tests, inflammatory markers, and basic metabolic chemistries.

Routine imaging is not recommended.

Polysomnography may be warranted if the patient has symptoms of obstructive sleep apnea.

Approach to the Patient

Fibromyalgia is a difficult and controversial diagnosis for many primary care providers. Patients are commonly referred to rheumatology specialists for management, though most rheumatologists do not

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provide primary care for fibromyalgia [14]. Published treatment guidelines recommend that management of patients with fibromyalgia should be carried out in the primary care setting [15].

Treatment

Treatment should be viewed through the biopsychosocial model of illness and directed at the cardinal symptoms of fibromyalgia. Hallmarks of treatment include patient education, exercise, management of coexisting conditions, and pharmacologic therapy. Patients respond best to multidisciplinary, individualized treatment programs such as those implemented in a patient-centered medical home management framework [14–16]. Self-efficiency should be a goal of treatment. Unfortunately, most patients with fibromyalgia continue to have some level of chronic pain and fatigue despite treatment but can continue to live normal and active lives.

Patient Education

Patient education and shared decision-making has been shown to have a beneficial effect on pain scores and decrease in overall resource use and healthcare costs [17]. Patients should be reassured that despite the uncertain pathogenesis, fibromyagia is a real disease process. They should be educated regarding the nature of centralized pain dysregulation and assured that fibromyalgia is a benign disease. Comorbid stress, mood, and sleep disorders should be acknowledged, and education about maladaptive chronic illness behavior should be considered.

Exercise

Exercise is strongly recommended as a treatment for fibromyalgia and has been shown to decrease pain and improve physical function and health-related quality of life [17, 18]. Patients should be counseled that they will likely experience a temporary increase in pain upon initiating an exercise regimen, but this can be mitigated by individualizing treatment programs based on patient preference and comorbidities. Cardiovascular fitness training and low-impact aerobic activities such as brisk walking, biking, swimming, and water aerobics are usually well tolerated. Exercise should be initiated at whatever intensity and duration is possible and gradually increased to a target of 30 min three times per week. Even if patients cannot achieve this goal, they should be encouraged to continue exercising at whatever level is tolerated. Specific written exercise "prescriptions" can be helpful, as adherence is generally poor without persistent health care coaching [1].

Behavioral and Coexisting Disorders

In patients with fibromyalgia, the lifetime prevalence of anxiety is 60%, and depression is 74% [1]. Chronic overlapping pain conditions are common and include functional somatic syndromes such as irritable bowel syndrome, chronic fatigue syndrome, headaches, bladder and pelvic pain syndromes, and temporomandibular disorders [19]. Inadequate management of these conditions can worsen pain directly or indirectly and adversely affect fibromyalgia severity. In addition to disease appropriate treatment of these comorbidities, cognitive behavioral therapy, mind-body therapies, and stress reduction techniques can be helpful.

Medications

Pharmacologic therapy should be started at low dose and titrated up slowly. In the case of inadequate response or intolerable side effects, alternative agents should be preferentially selected based on a patient's most prominent symptoms. Clinically significant improvement occurs in 25–45% of patients treated with medications [20]. Off-label use of medications is common.

The tricyclic antidepressant (TCA) amitriptyline is considered first-line therapy [21]. Other medication class options include tricyclic muscle relaxants, serotonin-norepinephrine reuptake inhibitors (SNRI), and anticonvulsants. Amitriptyline (Elavil) is started at 10 mg at bedtime and may be increased by 5 mg every few weeks. The common effective range is 20–30 mg with a maximum dose of 75 mg. Cyclobenzaprine (Flexeril) is started at 5–10 mg at bedtime and titrated up to 30–40 mg divided daily.

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Pregabalin (Lyrica), duloxetine (Cymbalta), and milnacipran (Savella) are the only drugs approved by the US Food and Drug Administration for treatment of fibromyalgia [1]. Pregabalin and gabapentin (Neurontin) are used to help patients with more severe sleep disturbances. Duloxetine and milnacipran can treat concomitant depression, fatigue, and pain symptoms.

Medications should be trialed for at least 3 months at the recommended dose before switching agents. Patients who respond to medication should be maintained on the lowest effective dose for at least 12 months. The decision to wean off medication should be individualized; many patients remain on medication indefinitely.

There is no evidence that acetaminophen (Tylenol), nonsteroidal anti-inflammatory drugs (NSAIDs), or opioid analgesics are effective in fibromyalgia. On the contrary, treatment with opioids results in poorer outcomes [22].

Myofascial Pain Syndrome

General Principles

Definition/Background

Myofascial pain syndrome (MPS) is a soft tissue pain disorder with symptoms similar to fibromyalgia. Both are characterized by painful trigger points; however MPS differs in that the trigger points are located in just one anatomic region rather than generalized, and the course is self-limited rather than chronic. MPS is not associated with fatigue or sleep disturbances.

Classification

MPS can be viewed as a spectrum of regional pain disorders. Myofasical trigger points can be caused by acute injury, repetitive microtrauma related to work or every day activities, or chronic strain of sedentary habits. Examples include whiplash injuries, occupational repetitive or overuse syndrome, non-specific low back and cervical strain, tension headaches, and temporomandibular joint syndrome [23].

Approach to the Patient

Diagnosis

History and Physical Examination

There are no universally accepted diagnostic criteria for MPS [23].

Patients typically complain of deep aching pain located in one localized area, centered around a specific trigger point. Myofascial trigger points can be palpated, usually within a tight band of muscle of fascia. Etiology of the pain should be investigated with a thorough patient history.

Treatment

MPS is treated similarly to fibromyalgia; however prognosis is better, and patients usually respond well to local treatments. The expected clinical course and prognosis should be described to the patient as early as possible. Heat and cold modalities, topical pain relief creams, and passive stretch are common first-line therapies with few adverse reactions. For refractory cases, trigger point injections with a local anesthetic or corticosteroid, dry needling, and prolotherapy have been shown to be effective [23].

As with fibromyalgia, if patients develop chronic symptoms, treatment should focus on patient validation, education, and self-efficiency.

Complex Regional Pain Syndrome

General Principles

Background/Classification

Complex regional pain syndrome (CRPS) is a chronic pain disorder characterized by regional soft tissue changes and disproportionately severe pain arising from a previous injury.

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Symptoms can include pain, swelling, decrease range of motion, sensory and vasomotor skin changes, and bone demineralization. This condition has also been referred to as reflex sympathetic dystrophy, causalgia, and transient osteoporosis [24].

The exact cause of CRPS is unknown but, like fibromyalgia, is suspected to be related to underlying central nervous system sensitization [25]. Common inciting events include fracture, soft tissue crush injuries, sprains, and surgery.

There are two recognized subtypes: type I and type II. In type I cases, there is no evidence of underlying nerve injury. This represents 90% of CRPS patients [24]. Type II refers to cases in which peripheral nerve injury is present. There are also "warm" and "cold" subtypes, referring to associated vasomotor skin symptoms, but these are not universally accepted.

Epidemiology

CRPS is more common in women than men, with an incidence of around 5–20 per 100,000 per year [25].

Approach to the Patient

Diagnosis

History and Physical Examination

The main symptoms of CRPS typically present within 4–6 weeks of an identifiable inciting event or injury. The most common complaint is pain. It is usually described as a continuous deep burning or tearing pain. Pain is usually associated with functional motor impairments including loss of strength or decreased range of motion. Patients may also complain of sensory or autonomic changes including differences in skin temperature, color, or edema. Trophic changes such as decreased hair growth, joint contraction, and skin atrophy may develop later in the course of disease [25].

Physical exam will typically reveal evidence of the inciting injury; however, the extent of symptoms should no longer be fully explained by the initial trauma. Findings will extend beyond the original region involved and cross through different nerve root distributions. Symptoms usually extend to the distal limb.

Laboratory and Imaging

There is no gold standard test to diagnose CRPS [24]. Plain radiographs or bone scintigraphy of the affected and contralateral limbs can be helpful to distinguish subtle bone changes.

Diagnostic Criteria

The Budapest Consensus Criteria aids in clinical diagnosis [26]. This includes:

- Continuing pain disproportionate to the inciting event
- Reports of one symptom in each of following categories:
  - Sensory: Hyperaesthesia or allodynia
  - Vasomotor: Temperature asymmetry, skin color changes, skin color asymmetry
  - Sudomotor: Edema, sweating changes, or asymmetry
  - Motor/trophic: Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), or hair/skin/nail changes
- Findings of one sign in two or more of the following categories:
  - Sensory: Hyperalgesia to pinprick or allodynia to light touch, temperature, deep somatic pressure, or joint movement
  - Vasomotor: Greater than one degree Celsius skin temperature asymmetry or skin color change or asymmetry
  - Sudomotor: Edema, sweating changes, or sweating asymmetry
  - Motor/Trophic: Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), or hair/skin/nail changes.
- And having no other diagnosis that that better explains the signs and symptoms.

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Differential Diagnosis

The variety of signs and symptoms of CRPS makes for a broad differential diagnosis. Common alternative causes include compartment syndrome, peripheral vascular disease, DVT, peripheral neuropathy, rheumatoid arthritis, erythromelalgia, conversion, and facticious disorders.

Prognosis and Treatment

The prognosis for CRPS is uncertain. Spontaneous resolution of symptoms has been described, but most patients have some degree of permanent disability. Spontaneous recurrence is also possible and can occur in a different limb than the original episode [25].

Due to the unpredictable course of the disease, goals of treatment focus on restoration of function, management of pain and disability, and improvement in quality of life.

A multidisciplinary approach including physical therapy (PT), occupational therapy (OT), psychosocial support, and pain management is recommended [24].

Referrals

PT and OT should be initiated as quickly as possible after diagnosis as treatment is more effective when begun early [24]. Patients should be instructed that the symptoms they experience are neutrally mediated and do not indicate tissue damage. It is important to note that most therapies utilized to rehabilitate the affected limb will likely result in some level of pain.

Referral to a pain management specialist is recommended in patients with progressive symptoms who have an unsatisfactory response to initial conservative measures. Trigger point injections can be effective and are safer than other interventional options. There is limited and conflicting evidence for sympathetic nerve blocks for treatment of CRPS. Spinal cord stimulators have not been shown to improve functional outcomes or improve pain scores [24].

Comorbid behavioral health disorders can interfere with rehab goals and should be addressed appropriately.

Medications

Pain medications should be used to the extent that it allows for active participation in the rehab process. Common first-line medication includes NSAIDs. Adjuvant medications such as gabapentin or pregabalin are used for neuropathic pain. Bisphosophonates can be effective in patients with evidence of abnormal bone scans. Calcitonin, glucocorticoids, and opioids have been prescribed but have a less favorable risk to benefit ratio [24].

Neuroma

General Principles

Definition/Background

Neuromas are painful benign nervous system tumors that develop as a result of nerve injury. When injured, nerve endings regenerate in an unregulated fashion, resulting in neuroinflammation and disorganized growth, forming a neuroma. Most are asymptomatic which makes incidence difficult to estimate, but studies have placed incidence after amputation between 1% and 7.8% [27]. They have potential to develop anywhere in the body, but several common locations have been described and named. Injury prevention and repair of intraoperative nerve injury are key strategies for management.

Classification

There are three categories of neuromas: neoplasms, traumatic neuromas, and neuromas as a part of a syndrome.

Examples of true neoplastic neuromas include vestibular or acoustic neuroma, nerve sheath myxoma, and others. Acoustic neuromas develop on the vestibular portion of the eighth cranial nerve and cause hearing loss, tinnitus, and sometimes vertigo. They are diagnosed with neuroimaging and can be treated by surgery and radiation [27].

Traumatic neuromas can develop from a sharp, blunt, or traction injury. They are common after elective hand or knee surgery. Stump neuromas can also develop after amputation. A Morton's

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neuroma is a specific traumatic interdigital neuroma of the foot. It causes burning pain in the intermetatarsal space, most commonly between the third and fourth metatarsals. They are diagnosed with ultrasound and are treated conservatively with metatarsal support devices, shoe inserts, and, if severe, intralesional steroid injection. Surgery is only required in refractory cases [27].

Neuromas can also occur as part of a syndrome. Neurofibromatosis is a genetic syndrome that results in the growth of multiple central and peripheral nervous system neuromas. Multiple endocrine neoplasia 2B involves the trio of mucosal neuromas, thyroid carcinoma, and pheochromocytoma.

Approach to the Patient

Diagnosis

History and Physical Examination

History will reveal some sort of trauma or recent surgery to the affected region. Patient complains include burning, tingling, numbness, or sharp pain. A hard lump is usually felt and can reproduce an electric shock sensation on palpation.

Imaging

Diagnosis is mainly reliant on history and physical exam. Plain radiographs are done to rule out underlying bone injury. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are rarely necessary.

Treatment and Prevention

Prevention is essential to management. Many neuromas form as a result of surgery, so surgeons should reconnect severed nerve endings intraoperatively wherever possible to prevent neuroma formation. Surgical repair should not be under tension. If the two ends cannot be rejoined, as in the case with amputation, it is common to bury the nerve into nearby muscle tissue for targeted muscle reinnervation.

In the case of already formed neuromas, there is no consensus on best treatment practice which can vary based on neuroma location and etiology. Ice packs and relative rest can alleviate symptoms. Pain is resistant to most pharmacologic therapy, yet prescriptions for NSAIDs and local anesthetic creams are common. Intralesional steroids are reserved for refractory cases. Surgical excision is an option but recurrence rates range from 15% to 50% [27].

Dupuytren's Contracture

General Principles

Background

Dupuytren's disease, also called Dupuytren's contracture, is a fibroproliferative disorder that results in shortening and thickening of the palmar fascia, leading to progressive and symptomatic flexion contracture of the fingers.

Epidemiology

Dupuytren's disease is most common in whites of Northern European descent. It is more common in men than women, and average age at onset is 60 years old. Studies have suggested an autosomal dominant with incomplete penetrance genetic inheritance pattern [24].

It is more prevalent in patients with diabetes and has been associated with smoking, increased alcohol intake, manual labor or exposure to vibrations, low body mass index, and some anticonvulsant drugs [28].

Approach to the Patient

Diagnosis

Physical Examination

Dupuytren's disease begins as a palpable palmar nodule and progresses to a thickened peritendinous band of tissue resulting in a flexion contracture of the fingers. It is most common in the fourth and fifth digits. Skin tethering, puckering, and pitting, dimpling, and tenderness of the skin are common.

The Hueston's tabletop test is a simple procedure that can assist in diagnosis. It is positive if the

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patient is unable to lay their fingers, palm down, flat on a table [28].

Imaging is not usually warranted, and the diagnosis can be made clinically.

Treatment

Treatment is indicated as the contracture shows signs of progression and begins to impair function. For mild cases, the nodule can be injected with steroids to slow progression. One study showed that intermittent triamcinolone acetonide (Kenalog) injections every 4–6 weeks for 4–5 months led to significant regression [29]. Enzymatic collagenase injections and percutaneous needle aponeurotomy are alternatives to surgery that are also being investigated.

Referrals

Surgical referral is warranted if the metacarpal phalangeal joint contracture is greater than 30° or if there is any contracture of the proximal interphalangeal joint. Surgery is usually successful but the recurrent rate is high [30].

Ganglion Cyst

General Principles

A ganglion cyst is a benign fluid-filled mass overlying a joint or tendon sheath. They can occur anywhere on the body but are most common in the hand and wrist. Seventy percent are found on the dorsal wrist, 20% on the volar wrist, and the remaining 10% at other body sites [31]. They are commonly diagnosed in the second to fourth decades of life with a female predominance.

Approach to the Patient

Diagnosis

Physical Examination

Ganglion cysts present as an obvious palpable firm, round, smooth mass overlying a joint line. If they are large enough to exert mass effect on surrounding structures, patients may complain of joint tenderness, decreased range of motion, sensory, or motor loss.

Differential Diagnosis, Imaging, and Special Testing

Transillumination is an easy technique that can be done in an office setting to help ganglion cysts from other soft tissue nodular lesions. Ganglion cysts will transilluminate, while epidermoid cysts, lipomas, rheumatoid nodules, and tenosynovial giant cell tumors will not [31].

Consider gouty tophi in patients with a history of gout.

Infectious tenosynovitis can present as periarticular swelling but is accompanied by redness and swelling and preceded by a puncture or bite wound.

Ultrasound and MRI can also be useful but are usually reserved for pre-surgical planning.

Treatment

Treatment includes surgical and nonsurgical options. Around 50% of ganglion cysts will resolve spontaneously with observation [31].

For symptomatic patients, simple in-office aspiration can be attempted; however, recurrence rates are over 50% at 1 year [31]. If the cyst recurs within 1 month after aspiration, repeat attempts are unlikely to be successful. If symptoms are controlled for a longer period of time, repeat aspiration can be considered.

Surgical referral is warranted in patients with persistent symptoms despite conservative therapy. Surgical resection is more effective than aspiration with a less than 10% recurrence rate [31].

Closed rupture of ganglion cyst or "bashing it with a bible" is not recommended.

Selected Disorders of Bone

Benign Tumors

General Principles

Nonmalignant bone tumors are often discovered incidentally during evaluation for a different condition. When symptomatic, patients may

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complain of pain or swelling which can easily be confused for other musculoskeletal ailments which contribute to a delay in diagnosis.

Age of presentation, pain characteristics, and radiographic appearance can help assist in diagnosis. Treatment of these benign tumors ranges from observation to surgical removal.

Osteoid Osteoma

Background

Osteoid osteoma is a bone-forming tumor characterized by a small nidus of reactive bone identified on XR. It accounts for 12% of all benign bone tumors and is most common in the second decade of life. It is 2–3 times more common in males than females [32]. It is typically found in the long bones: femur, tibia, and humerus. Less commonly it presents in the posterior element of the spine.

History and Physical

Osteoid osteoma has a classic presentation of nocturnal bone pain dramatically improved with aspirin or NSAID medications [33]. Depending on the site, patients may also present with limp, leg-length discrepancy, localized swelling, and tenderness.

Imaging

Radiographs will show a small, less than 2 cm (0.75 in.), round osteolytic nidus surrounded by bone sclerosis. This is classically found in the cortex. About 25% of cases will present with a "target pattern" of central ring-like calcification [32].

Treatment and Prognosis

Treatment depends on symptoms. If pain can be managed with NSAID medication, observation with serial radiographs every 4–6 months is reasonable. Treatment for symptomatic lesions includes surgical resection or percutaneous radiofrequency ablation of the nidus. Untreated osteoid osteomas will spontaneously resolve over the course of months to years [34].

Osteochondroma

Background

Osteochondroma is a cartilage-capped bony overgrowth arising from the surface of a bone. It is the most common primary bone tumor, accounting for 30% of benign bone tumors. It is most common in the second decade of life and is 1.5 times more common in males [35]. It has a predilection for the distal femur, proximal humerus, and proximal tibia.

History and Physical

Osteochondromas typically present as a painless palpable mass on the axial skeleton. They may cause pain and swelling if fractured. They may rarely grow large enough to compression of local neurovascular structures.

Imaging

Radiographs are sufficient for diagnosis. The bony protuberance can be pedunculated or sessile, typically growing away from the epiphysis and toward the diaphysis. The cartilage cap is thicker in childhood and progressively narrows into adulthood [35].

Treatment and Prognosis

Most osteochondromas do not need treatment. They continue to grow through adolescence and stop growing as the growth plate closes. There is a small lifetime risk of malignant transformation to chondrosarcoma, especially if the cartilage cap is greater than 2 cm (0.75 in.) thick or if it is

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increasing in size after skeletal maturity [33]. In these cases, treatment is surgical excision of the entire cartilage cap.

Enchondroma

Background

Enchondroma is a cartilage-forming neoplasm found in the marrow cavity. It is more common in women and can be found any time from the second to sixth decades of life with a peak in the in the 30s and 40s. They usually occur in the long bones with a predominance for the hands [36].

History and Physical

The majority of enchondromas are asymptomatic and are found incidentally. Pathologic fractures are more common with lesions in the hands and feet [36].

Imaging

Enchondromas are sharply defined and oval shaped. Endosteal scalloping and calcifications are common [33].

Treatment and Prognosis

Enchondromas are usually self-limited. If they require excision, simple curettage is sufficient. Recurrence is rare.

Non-ossifying Fibroma

Background

Non-ossifying fibroma is a developmental cortical defect, or "bone scar," in which normally ossified areas are instead filled with a fibrous connective tissue. They present in the second decade of life with no gender predominance. They are most common in the tibia and fibula [36].

History and Physical

These lesions are asymptomatic and are usually discovered during workup for unassociated trauma.

Imaging

Non-ossifying fibromas are small, irregular lytic lesions with sclerotic scalloped borders. They may have a more atypical appearance as they fill in with normal bone and resolve.

Treatment and Prognosis

They do not require any further treatment of follow-up. They fill in during adolescence and rarely recur.

Malignant Tumors

General Principles

Malignant bone cancers account for less than 1% of diagnosed cancers each year. Delay in diagnosis is common due to their rarity and the frequency of other musculoskeletal complaints. Lesions are often discovered during workup for suspected fracture rather than bone malignancy. Plain XR imaging is the first diagnostic step and is often sufficient for diagnosis. Due to the significant morbidity and mortality involved, prompt referral to orthopedic cancer specialists is recommended [37].

Approach to the Patient

History and Physical

The primary presenting symptom of a malignant bone cancer is pain, tenderness, and decreased range of motion. Unexplained relapsing and

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remitting fevers may also be present. Nighttime pain is commonly cited but is only present in 20–30% of patients with a primary malignant bone tumor [38].

Diagnosis

Plain radiograph is the preferred primary imaging study for malignant bone tumors. Any XRs which show potential malignancy should prompt advanced imaging. MRI is superior to CT for evaluating local metastasis. Bone scans and chest CT are helpful for identifying systemic metastasis.

Early referral to a comprehensive cancer center can maximize survival and quality of life [39]. Biopsy confirms the diagnosis, establishes tumor grade, and helps direct treatment.

Primary Osteosarcoma

Background

Osteosarcoma originates from malignant mesenchymal stem cells that differentiate into osteoblasts, the normal bone-forming cells. It is the most common bone cancer and the third most common childhood malignancy. Lesions classically develop in the metaphyses of long bones at the growth plate and thus tend to occur at the age of maximum bone growth. Median incidence is from 12 to 16 years old. Tumors can metastasize regionally or systemically and most often metastasizes to the lungs or to the bones of another extremity [40].

Osteosarcoma is associated with a few specific risk factors. The genetic syndromes Li-Fraumeni syndrome and retinoblastoma have higher incidence of osteosarcoma. History of radiation, previous implanted metal orthopedic prostheses, and Paget disease all have increased risk [39].

Imaging

Osteosarcoma is characterized radiographically by dense sclerosis of the metaphysis. Most tumors extend into the soft tissue and have radiating calcification in a "sunburst" pattern. Both osteosclerotic and lytic lesions can be present [39].

Treatment and Prognosis

Current treatment for osteosarcoma includes preoperative chemotherapy, surgical resection, and postoperative chemotherapy. This approach has helped 90–95% of patients with osteosarcoma avoid limb amputation [37]. Neoadjuvant chemotherapy can decrease the size of the primary tumor size and any pulmonary metastases, while adjuvant chemotherapy helps decrease risk of postsurgical metastasis. Radiation therapy is rarely used.

Five-year survival rate is more than 70% in people with non-metastatic disease but less than 30% if metastases are present. Unfortunately, nearly 20% of patients initially present with lung metastases [41]. Metastatic lesions that remain after chemotherapy are often surgical resected.

Ewing's Sarcoma

Background

Ewing's sarcoma is the second most common type of bone cancer. Its cell origin is unknown, but it is classified in a group of tumors known as small blue round cell tumors.

Like osteosarcoma, this cancer primarily affects children and adolescents during the period of peak bone growth. Unlike osteosarcoma, it typically affects the pelvis, diaphysis of long bones, ribs, and scapula. Common sites of metastasis include the lungs and other bones. There are few known risk factors for Ewing's sarcoma, though it has been associated with some specific genetic translocations [40].

Imaging

Radiographic appearance of Ewing's sarcoma is characterized by bone destruction. Radiating calcification "sunburst" pattern and lamellated

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"onion skin" periosteal reaction can be seen but are not pathognomonic [39].

Treatment and Prognosis

Like osteosarcoma, treatment for Ewing's sarcoma is neoadjuvant chemotherapy, surgical resection, and adjuvant chemotherapy. However, the use of radiation therapy is effective as an alternative therapy for lesions not amenable to surgical resection.

Metastasis at the time of diagnosis is the most significant negative prognostic factor for Ewing's sarcoma. Survival rates are comparable to osteosarcoma [41].

Chondrosarcoma

Background

Chondrosarcoma is malignant cartilage-producing tumor. It is the least common bone cancer. It usually manifests in people in their fifth to eighth decades of life and affects the central skeleton: pelvis, vertebrae, and proximal long bones. It can develop through malignant transformation of other benign cartilage tumors such as enchondromas [39].

Imaging

Plain radiographs may suggest the presence of a chondrosarcoma based on location and lesion appearance, but CT scan is optimal for evaluating tumor size and local extension. Typical XR appearance is an eccentric calcified osteolytic lesion, and CT can differentiate between mineralized and unmineralized cartilage matrix [29].

Treatment and Prognosis

Chondrosarcoma is generally resistant to chemotherapy. Surgical resection is the primary treatment. Radiation is reserved for lesions where surgical margins cannot be achieved. Tumor grade is the major prognostic indicator in chondrosarcoma. The vast majority of these tumors are low grade and survival rates after surgical resection are favorable [40].

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Part XXIII

The Skin and Subcutaneous Tissues

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Common Dermatoses

120

Wanda Cruz-Knight

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General Principles

According to a study conducted by the American Academy of Dermatology, one in every four people who present to a primary care physician (PCP) will have a skin-related problem; roughly 85 million Americans have skin disorders [1]. Therefore, skin conditions are a common cause of patient visits in the primary care setting. While most presentations are minor or easily identifiable, PCPs must be able to promptly recognize these conditions to determine appropriate management.

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Diseases of the integumentary system include everything related to the surface of the body. Table 1 outlines the most common skin disease categories and their types based on the International Classification of Diseases, Ninth Revision (ICD-9) and billing data from 2013 [1].

The dermatoses are divided into conditions affecting the skin, nails, and hair. This chapter will focus on the most common dermatoses. While common dermatoses may be accompanied by inflammation, the term dermatitis refers to inflammation of the skin and is not synonymous with dermatoses [2]. Causes of dermatosis may be multifactorial or unknown; most commonly dermatoses are categorized into autoimmune disorders, bacterial, fungal, viral, and genetic. The most common autoimmune disorders are vitiligo, lupus, and alopecia areata. *Staphylococcus aureus* and *Streptococcus pyogenes* are the most common bacterial. Tinea can cause skin infections such as athlete's foot. Ashy dermatosis is

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Table 1 Common skin disease categories and their types based on the International Classification of Diseases, Ninth Revision (ICD-9) and billing data from 2013

Disease category	Disease type
Acne	Acne
Atopic dermatitis/eczema	Atopic dermatitis; eczema; dyshidrosis
Actinic damage	Actinic keratosis; solar dermatitis; sunburn; actinic dermatitis
Bullous diseases	Dermatitis herpetiformis; pemphigus; pemphigoid; other bullous dermatoses; erythema multiforme
Congenital abnormalities	Various hereditary and congenital conditions and anomalies, including ichthyosis congenita, vascular hamartomas, and congenital ectodermal dysplasia
Connective tissue disorders	Lupus; dermatomyositis; scleroderma; diffuse connective tissue disease
Contact dermatitis	Contact dermatitis; diaper rash; nonspecified dermatitis
Cutaneous infections	Bacterial skin infections, including tuberculosis and leprosy; cellulitis; carbuncles; impetigo; onychia
Cutaneous lymphoma	Mycosis fungoides/Sezary syndrome; parapsoriasis
Drug eruptions	Drug dermatitis; Stevens-Johnson syndrome
Hair and nail disorders	Alopecia; telogen effluvium; hirsutism; hair and nail anomalies
HPV/warts/molluscum	Warts, including genital warts; molluscum contagiosum
Melanoma	Malignant melanoma
Nonmelanoma skin cancer	Basal cell carcinoma; squamous cell carcinoma; Kaposi sarcoma; carcinoma in situ
Noncancerous skin growths (benign neoplasms/keloids/scars/cysts)	Lipomas; benign neoplasms; hemangiomas; chalazions; cysts, including pilonidal, Pilar, and sebaceous; corns, calluses, and keratoderma; keloids; scars and fibrosis
Pruritus	Pruritus not otherwise specified; psychogenic skin disease; lichenification
Psoriasis	Psoriasis
Rosacea	Rosacea
Seborrheic dermatitis	Seborrheic dermatitis
Seborrhea	Seborrheic dermatitis; blepharitis
Ulcers	Ulcers, all stages and causes; pyoderma gangrenosum
Urticaria	Psoriasis
Viral	Fungal diseases herpes simplex; herpes zoster; viral exanthemata; dermatophytosis; dermatomycosis; candidiasis
Vitiligo	Vitiligo
Wounds and burns	Burns, all degrees; lacerations; wounds; abrasions; bites; foreign bodies, e.g., splinters

commonly caused by HIV. Finally, genetic susceptibility can predispose people to dermatoses.

There are many skin-related disorders. This chapter will focus on common conditions that most primary care providers will encounter and manage.

Acne

Acne vulgaris is the most common skin condition in the United States, affecting 20% of young people [3]. The severity of acne correlates with puberty, although acne may persist into the 20s and 30s in 64% and 43% of individuals, respectively [3]. Acne can affect the skin in varying degrees from mild involvement to severe presentations leading to facial disfigurement, scarring, and hyperpigmentation. Adolescents and young adults with acne often struggle with the psychosocial effects of acne and may have a higher rate of depression [4].

The pathogenesis of acne vulgaris is complex. Originating within the pilosebaceous follicles, there are four main processes involved in the production of comedones or microcomedones

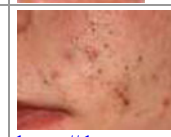
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that lead to pimples, papules, or skin scarring, sebum overproduction in the follicles, abnormal shedding of follicular epithelium, follicular colonization by *Cutibacterium acnes*, and inflammation [5]. Excessive androgen hormones or hypersensitivity of sebaceous glands to normal levels of androgen is believed to be the cause of sebum overproduction, with activation of the inflammatory pathway at all stages of acne progression [6]. Genetic factors, diet, psychological stress, tobacco smoke, and damage to the skin integrity may also be involved in the development or progression of acne.

Clinical manifestations of acne vary dependent on type. Table 2 describes the different types of acne lesions; the extent and severity of skin lesions vary widely depending on inflammatory nature and body's response to follicular irritation

Table 2 Clinical manifestation: acne vulgaris occurs in areas of the body with hormonally responsive sebaceous glands such as the face, neck, chest, upper back, and upper arms

Types of acne lesions	Description	Image	Examples
Non-inflammatory acne			
Closed comedones	<5 mm; dome-shaped; smooth; skin-colored, whitish, or grayish papules		Whiteheads
Open comedones	<5 mm papules with a central, dilated, follicular orifice containing gray, brown, or black, keratotic material	 https://dermnetnz.org/topics/comedonal-acne/	Blackheads
Giant comedones	>5 mm papules, sebaceous material in pores usually black/brown		Large blackhead-appearing lesions
Solar comedones	Small skin-colored papule from sun damage and usually form in older adults, primarily on the cheeks	 https://dermnetnz.org/topics/comedonal-acne/	Mixed white and black sebaceous material
Inflammatory acne			
Papulopustular acne	<5 mm inflamed, relatively superficial papules and pustules		Pus-filled pustules
Nodular acne	>0.5 mm pustules or >1 cm nodules that are deep-seated, inflamed, often tender		Nodular acne

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Table 3 Differential diagnosis of acne vulgaris

Inflammatory facial lesions	Non-inflammatory facial lesions	Trunk and extremities	Acneiform eruptions
Rosacea	Sebaceous hyperplasia/ seborrheic dermatitis	Folliculitis	Drug-induced acne
Periorificial dermatitis	Nevus comedonicus	Keratosis pilaris	Neonatal cephalic pustulosis
Pseudofolliculitis barbae	Adnexal tumors	Hidradenitis suppurativa	Acne cosmetica
Facial angiofibromas in tuberous sclerosis	Favre-Racouchot syndrome	Steatocystoma multiplex	Acne mechanica
Acne fulminans	Miliaria	Acne fulminans	Occupational acne and chloracne

and activation of inflammatory pathways. Treatment options are based on individual presentation and extent and severity of skin involvement.

Approach to the Patient

Diagnosis of acne vulgaris is dependent on history and physical examination. While there are no laboratory tests to confirm a diagnosis of acne, testing may be warranted when there is suggestion of underlying hyperandrogenism, abscess formation, or other conditions needing additional testing. Patient history is an important element of identifying risk factors that may promote/exacerbate acne formation or guide treatment options.

Patients should be asked information regarding:

- Onset of acne.
- Current medications (there are medications that can exacerbate acne).
- Menstrual history (females) and association with menstrual cycle [7].
- Family history of acne (there is a familial predisposition to acne).
- Systemic symptoms, joint pains, myalgias in patients with severe acne.
- Questions regarding virilization.
- Medical history to include history of prior acne treatment and response.
- Skin care regiment.
- Psychosocial impact.

On physical examination, attention to lesion type and distribution, signs of hyperandrogenism in young children and females, and the presence of skin scarring and post-inflammatory hyperpigmentation are important factors in determining extent/severity of acne, ruling out other skin conditions that may mimic acne, and guiding treatment options. The differential diagnosis of acne can be approached based on location of lesions, onset and duration, and inflammatory versus non-inflammatory nature; Table 3 will outline some of these conditions.

Treatment Options

Treatment of acne vulgaris is based on severity of lesions, location on the skin, and hormonal and dietary history. The decision to use a topical versus an oral therapeutic approach is also dependent on presentation and individual history. Topical treatment options may be available over the counter and by prescription dependent on the formulation and strength needed when individualizing the therapeutic plan [8]. Topical agents are divided into bacteriostatic and bactericidal and are widely available in different formulations and strengths [9, 10]. It is recommended that topical antibiotics not be used as monotherapy due to increased risk of resistance to *C. acnes*. The treatment is aimed at counteracting follicular hyper-proliferation and sebum production, decreasing the levels of

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C. acnes on the skin surface, and attacking the inflammatory pathways. Topical retinoids, benzoyl peroxide, azelaic acid, and salicylic acid are effective against comedone formation, with retinoids being preferred as first-line therapy [11]. For patients with mild to moderate inflammatory acne, a topical antibiotic should be added to benzoyl peroxide therapy, as the treatment has been shown to be more effective [9]. For patients with moderate to severe inflammatory acne, an oral antibiotic is recommended along with the use of a topical retinoid and benzoyl peroxide [11].

Oral isotretinoin is reserved for patients with severe, recalcitrant, nodular acne. While women with signs of hyperandrogenism once evaluated for other conditions may benefit from use of oral contraceptives. It is recommended that oral antibiotics be used for limited therapeutic courses, up to 3–4 months. Topical retinoids may be used for acne prevention. A skin care regiment is also an important component of treatment. Use of gentle cleansers and selection of noncomedogenic skin care products and cosmetics are recommended. Facial peels and other cosmetic treatments target hyperpigmentation and scarring and help to improve the psychosocial impact of acne. Referral to a dermatologist is recommended for recalcitrant acne or failed treatment with appropriate management.

Atopic Dermatitis

Atopic dermatitis also known as eczema is an inflammatory skin disease that includes skin dryness, erythema, oozing, and crusting that can lead to lichenification of the skin [12]. While the causes of eczema are not clear, it is believed to be due to genetic predisposition to environmental allergens with skin destruction from pruritus causing much of the disease burden of patients and family. Atopic dermatitis affects up to 25% of children and 2–3% of adults [13]. One out of ten people will develop eczema in their lifetime, with 60% of those predisposed becoming symptomatic in their first year of life and 90% before the age of 5 [14].

Approach to the Patient

History, onset, and clinical presentation are key diagnostic tools. While pruritus is the hallmark for diagnosis, eczema, age of onset, and location of dry skin in skin folds are other criteria [15]. Identifying triggers improves burden of disease. There are no specific labs to aid in diagnosing eczema, although skin biopsy for atypical presentations. Allergy testing can aid with treatment options.

Treatment

Treatment of atopic dermatitis is dependent on severity, skin involvement, causative agents if identified, and medical history. The goal of treatment is reduction of symptoms and prevention. Reducing inflammatory response with topical anti-inflammatory preparations and protecting skin with barriers that prevent cracking and dry skin are important. Patients with severe or refractory eczema may require autoimmune modulators, phototherapy, or systemic treatment [16].

Other common dermatoses are listed in Table 4.

Family and Community Implication of Common Dermatoses

The overall burden of diseases that make up the dermatoses is significant. Yearly over $80 billion healthcare dollars are spent on management of these diseases [20, 21]. Likewise, many of the dermatoses cause skin scarring and deformities that have psychological implications. The chronic condition of some of the dermatoses discussed also affects quality of life and increases burden of suffering. Treatment options continue to improve as research and development continue to address the need for improved management of diseases that make up common dermatoses.

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Table 4 Other common dermatoses

Common dermatosis	Epidemiology	Approach to the patient	Diagnosis	Treatment
Androgenetic alopecia, also referred to as hereditary thinning or balding	Affects about 50 million men and 30 million women [17]	Clinical and family history counseling and management of psychosocial implications	Family history Diffuse hair thinning over the central scalp, while the frontal hairline is usually retained in women Gradual recession of the frontal hairline, gradual thinning in the temporal areas, producing a reshaping of the anterior part of the hairline in men Labs: Dehydroepiandrosterone (DHEA) sulfate and testosterone analysis	Identifying and treating other causes of hair loss, i.e., fungal, damage from hair products, thyroid disorders, or iron deficiency Minoxidil: Androgen-independent hair growth stimulator Finasteride: 5-alpha reductase type 2 inhibitors Hair transplant/plugs Hormones to correct imbalance
Psoriasis	Over seven million Americans affected [18] Occurs in all age groups but has the highest prevalence among ages 45 and 64	Clinical and family history – a complex immune-mediated disease in which T lymphocytes, dendritic cells, and cytokines (interleukin [IL]-23, IL-17, and tumor necrosis factor [TNF]) play a central role	Clinical presentation of erythematous papules and plaques with silver scale, may also be accompanied by joint pain and other systemic symptoms No available labs except to exclude other differential diagnosis Skin biopsy if history and physical exam is inconclusive Differential diagnosis may include seborrheic dermatitis, atopic dermatitis, lichen chronicus, fungal infections	Address psychosocial aspect Mild to moderate disease responds to topical corticosteroid therapy, retinoid therapy, or phototherapy; topical tacrolimus or pimecrolimus may be used as alternatives or as corticosteroid-sparing agents for facial involvement Severe psoriasis requires phototherapy or systemic therapies such as retinoids, methotrexate, cyclosporine, apremilast, or biologic immune-modifying agents
Rosacea	Over 16 million Americans affected [19] Common among white people of all ages and races with these groups more commonly affected: Ages 30 and 60 Faired skin, blond hair, and blue-eyed individuals Menopausal women Family history of rosacea	Family history, history of onset and exacerbating factors, psychosocial implications	Diagnosis is based on clinical presentation and history Persistent centrofacial redness, phymatous skin changes (e.g., rhinophyma), papules, pustules, flushing, telangiectases, burning or stinging sensations, edema, and skin dryness Ocular involvement may include lid margin telangiectases, conjunctival injection, ocular irritation, or other signs and symptoms	Psychosocial Mild to moderate disease treated with topical metronidazole, azelaic acid, and topical ivermectin Oral antibiotic therapy, tetracycline, doxycycline, and minocycline are indicated for severe rosacea

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Skin Infections and Infestations

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Micah Pippin

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Bacterial Infections of the Skin

Impetigo

General Principles

Impetigo is a common bacterial infection affecting the superficial epidermis resulting in bullous and non-bullous skin eruptions.

Epidemiology

While children ages 2–5 are the most frequently affected, impetigo can manifest in persons of any age. *Staphylococcus aureus* and group A beta-hemolytic *Streptococcus pyogenes* are responsible for most cases; however, anaerobic bacteria are also implicated in disease development. The non-bullous subtype comprises a majority of cases, while bullous impetigo has a lower incidence and is caused exclusively by *Staphylococcus* and its epidermolytic toxins [1]. Certain medical comorbidities, such as diabetes mellitus, may predispose patients to impetigo.

Diagnosis

History and Physical Examination

The non-bullous form can be further categorized into primary, affecting intact, healthy skin, and secondary, infecting a previously disrupted epidermis. Diagnosis is clinical and based on a typical presentation and skin manifestation. An initial maculopapular lesion gives way to thin-walled vesicles that rupture and produce the characteristic honey-colored crusts. The typical distribution includes the nares and perioral area, with the extremities also being affected. Bullous impetigo is more often seen on the trunk, axilla, and intertriginous locations. Large, fluid-filled blisters collapse into flaccid bullae with a resulting thin, brown crust. Both bullous and non-bullous lesions are usually self-limited and resolve without scarring.

Treatment

Topical antibiotics, such as mupirocin, have demonstrated increased effectiveness versus placebo in the management of impetigo. Diffuse or severe infections and outbreaks may require systemic treatment; however, adverse effects and emerging antimicrobial resistance to oral antibiotics make topical therapies preferable. Specifically, oral penicillin and macrolides are no longer indicated due to resistance. There is currently insufficient evidence to recommend topical disinfectants or popular herbal treatments for impetigo [1]. The most serious complication is acute post-streptococcal glomerulonephritis; however, there is no data to support antibiotics as effective prevention of impetigo's nephritogenic potential [1, 2] (Fig. 1).



Fig. 1 Impetigo of the face

Erysipelas

General Principles

Erysipelas, historically known as "St. Anthony's Fire," is a bacterial skin infection of the dermis and lymphatics, often affecting the lower extremities and face and presenting similarly to cellulitis.

Epidemiology

Group A Streptococci is the most common causative organism entering through breaks in the skin and disseminating through the lymphatic system. Risk factors for erysipelas include obesity, diabetes mellitus, venous insufficiency, lymphedema, and any disruption of the cutaneous protective barrier [2, 3].

Diagnosis

History and Physical Examination

Fevers, chills, and malaise often precede the characteristic painful rash featuring an area of

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well-demarcated erythema with raised edges. The lower extremities are predominantly affected, while facial erysipelas also occurs and may develop secondary to nasopharyngeal streptococcal infection [2, 3]. Linear streaks of erythema may represent progression through the lymphatic system. The rashes' sharp margins help distinguish erysipelas from the deeper and less confined cellulitis infection.

Treatment

Antibiotics with coverage for streptococci should be administered with penicillin being first-line treatment. Most patients can be managed outpatient with oral preparations; however, severe infections may require intravenous antibiotics and hospitalization (Fig. 2).

Cellulitis

General Principles

Similar to erysipelas, cellulitis is an acute bacterial infection affecting the dermis; however, it also invades deeper into the skin's subcutaneous tissues.

Epidemiology

The majority of cellulitis presentations are attributed to the Gram-positive cocci *Streptococcus* and *Staphylococcus aureus*. In the case of animal bites, Gram-negative bacteria have been isolated. Methicillin-resistant *Staphylococcus aureus* (MRSA) is continuing to grow as a cellulitis pathogen.



Fig. 2 Erysipelas of the lower extremity

Any event or condition that compromises the integrity of the skin such as trauma, venous insufficiency, lymphedema, tinea pedis, diabetes, or obesity may increase susceptibility to acquiring cellulitis.

Diagnosis

History and Physical Examination

Typical findings suggestive of cellulitis include an area of erythema, pain, edema, and heat, most often occurring in a lower extremity. The findings are more diffuse than erysipelas and lack the sharply demarcated border. Purulence suggests *Staphylococcus aureus* as the etiologic organism. Systemic symptoms such as fever and malaise may accompany the cutaneous manifestations.

Evaluation

In general, clinical evaluation is sufficient for diagnosis; however, laboratory analysis and blood cultures should be pursued if sepsis is suspected. Inspection for the presence of an abscess is a vital component of the physical examination and can be difficult. In recent years, ultrasound has emerged as an effective technique in discovering abscess formation [4, 5].

Treatment

In cases of mild, uncomplicated cellulitis, oral antibiotics with coverage for *Streptococcus* and methicillin-sensitive *Staphylococcus aureus* (MSSA), such as cephalexin, should be initiated. If purulence is noted, or risk factors for MRSA are present, coverage for resistant *Staphylococcus* is needed and can be achieved with the addition of oral trimethoprim/sulfamethoxazole or clindamycin. Orbital cellulitis, a variant affecting the tissue surrounding the eye, mandates inpatient treatment and consultation with ophthalmology [2]. Severe cellulitis infections and patients with signs of sepsis or shock should also be treated inpatient with broad-spectrum intravenous antibiotics. Individual patient history and local

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Fig. 3 Cellulitis of the lower extremity

resistance patterns should direct treatment choices and augment standard guidelines (Fig. 3).

Folliculitis

General Principles

Folliculitis is a superficial inflammation of the hair follicles caused by infection and less frequently chemicals or trauma.

Epidemiology

Bacterial pathogens are most often responsible for folliculitis, and, of these, *Staphylococcus aureus* is the most prevalent. *Pseudomonas aeruginosa* may be encountered after exposure to unsanitary bathing reservoirs, and the resulting infection is frequently referred to as "hot tub folliculitis." There are significantly fewer folliculitis cases of fungal etiology, most of which are reported in patients with travel history or immunodeficiency. There may be a male gender preference for folliculitis secondary to frequent shaving.

Diagnosis

History and Physical Examination

A folliculitis diagnosis is clinically attained by observation of perifollicular papules and pustules with a surrounding ring of erythema. The lesions may be asymptomatic to painful depending on the degree of inflammation and can occur anywhere hair follicles are present.

Evaluation

Cultures may be obtained in recalcitrant cases; however, they are rarely required.



Fig. 4 Folliculitis

Treatment

Topical mupirocin and fusidic acid are first-line therapies for uncomplicated cases. Diffuse, resistant, or recurrent infections should be treated with oral antibiotics such as cephalexin or dicloxacillin. If MRSA infection is suspected or confirmed by culture, trimethoprim/sulfamethoxazole, clindamycin, or doxycycline may be administered systemically [2]. *Pseudomonas* folliculitis is generally self-limited, and antibiotic treatment is not warranted (Fig. 4).

Furuncles and Carbuncles

General Principles

Furuncles and carbuncles, also known as boils, can be viewed as an intermediate in the continuum of skin infections from folliculitis to abscess. While folliculitis affects the superficial tissue around hair follicles, furuncles invade deeper into the subcutaneous tissue and may develop an accumulation of purulent material. Carbuncle refers to an aggregation of individual furuncles resulting in a more diffuse eruption.

Epidemiology

Staphylococcus aureus, often inhabiting healthy skin and the nares, is the most common causative organism and is seeded in the hair follicle through disruptions of the protective cutaneous barrier. Conditions that compromise skin integrity, such as eczema, diabetes, obesity, and poor hygiene, predispose patients to infection [2, 6]. Young

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adults and males exhibit an increased predilection for furuncle and carbuncle formation.

Diagnosis

History and Physical Examination

Furuncles present as a tender, erythematous, fluctuant, nodule with superficial pustule formation. Carbuncles are clustered furuncles affecting a larger area and with multiple, purulent drainage sites. Any region of skin occupied by hair follicles can host these infections; however, the neck, face, axilla, groin, back, and buttocks are the most favorable sites of outbreak. Associated lymphadenopathy may manifest and systemic, constitutional symptoms such as fever and malaise can accompany localized inflammation.

Evaluation

The diagnosis can be made based on history and physical examination; however, cultures of expressed purulent material are often obtained to guide management strategies.

Treatment

The mainstay of treatment is incision and drainage of the lesion or lesions and may require subsequent initiation of empiric oral antibiotics. The same categories of antibiotics implemented for folliculitis are utilized, such as cephalosporins or dicloxacillin. If an MRSA etiology is suspected or cultured, antibiotic coverage should be selected to target this organism. Adjunctive topical antibiotics may be offered (Fig. 5).



Fig. 5 Carbuncle of the face

Hidradenitis Suppurativa

General Principles

Hidradenitis suppurativa is a chronic and progressive inflammatory condition of the follicular pilosebaceous units located in intertriginous areas. Along with the extensive somatic complaints associated with hidradenitis suppurativa, significant psychologic impact is observed, resulting in an increased adverse impact on quality of life compared to other dermatologic conditions [7].

Epidemiology

Hidradenitis suppurativa has a female predominance and occurs more frequently in blacks and patients with a personal family history. Disease onset is common to young adulthood, and there is an increased incidence in cigarette smokers and the obese. Associated conditions include diabetes mellitus, metabolic syndrome, polycystic ovarian syndrome, and Crohn disease [7].

Diagnosis

History and Physical Examination

Localized painful nodules are present in the mild form of hidradenitis suppurativa and may progress to abscess formation and a broadened distribution in moderate disease. The axillae are the most commonly involved sites, with the gluteal folds, groin, perianal area, perineum, and inframammary regions also affected. Diffuse and recurrent sinus tracts, scarring, and contractures occur in the severe manifestation of the condition. The Hurley classification system is implemented to clinically stage the severity of hidradenitis suppurativa and direct treatment strategies [7].

Treatment

Lifestyle modification, including weight loss and smoking cessation, are the primary non-pharmacologic treatments for hidradenitis suppurativa. Topical clindamycin is the first-line management for mild disease and may be combined with oral tetracycline for moderate presentations. Biologics, specifically adalimumab, are indicated for severe or recalcitrant disease, at

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which point, dermatology referral would be warranted [7]. Surgical measures, including punch debridement and incision and drainage, may be performed for acute relief; however, wide excision is the definitive treatment. Combinations of these treatment modalities may be implemented and are often indicated.

Screening for depression should be performed, and resources for the patient's psychological well-being should be made available [7] (Fig. 6).

Abscess of Skin

General Principles

A skin abscess is an accumulation of purulent material within the skin and subcutaneous tissues resulting in a painful and inflammatory focus of infection.

Epidemiology

Staphylococcus aureus, whether MSSA or MRSA, are the predominant bacteria responsible for cutaneous abscesses. Risk factors for abscess formation are similar to cellulitis, furuncles, and carbuncles and include breaks in the skin, venous insufficiency, immunosuppression, diabetes mellitus, and obesity. Abscesses can affect any demographic.



Fig. 6 Axillary hidradenitis suppurativa

Diagnosis

History and Physical Examination

Classic findings of erythema, tenderness, induration, and fluctuance are generally sufficient to make the diagnosis. Common locations for abscess formation include the extremities, axillae, groin, and buttocks [8].

Evaluation

If the physical examination is ambiguous, and the diagnosis is in question, ultrasound evaluation has demonstrated efficacy in distinguishing an abscess from cellulitis [8, 9]. Laboratory analysis is merited if signs of sepsis are present such as fever and tachycardia.

Treatment

Incision and drainage are required for successful treatment of cutaneous abscesses. Guidelines have stated that antibiotic use is unnecessary following successful surgical debridement of uncomplicated abscesses; however, new evidence suggests that the addition of oral antibiotics improves infection resolution rates and decreases recurrence risk. Also, in the case of complicated abscesses, of concurrent cellulitis, or when systemic symptoms manifest, antibiotic initiation is encouraged. If antimicrobials are implemented, coverage of MRSA with trimethoprim/sulfamethoxazole or clindamycin is recommended. Cephalosporins have not demonstrated effectiveness and are not suggested [8]. After incision and drainage of a typical abscess, packing is no longer advised as it has been shown to increase discomfort and has no effect on recurrence.

Prevention of bacterial skin infections such as folliculitis, furuncles, carbuncles, and abscesses through decolonization with intranasal mupirocin and topical chlorhexidine washes has been suggested; however, the efficacy of these measures has not been substantiated by statistically significant evidence (Fig. 7).

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Fig. 7 Abscess of the back

Necrotizing Fasciitis

General Principles

Necrotizing fasciitis is a rare, limb- and life-threatening, rapidly invasive infection of the subcutaneous tissue and fascia.

Epidemiology

Most cases are secondary to a polymicrobial bacterial infection; however, different subtypes of necrotizing fasciitis are monomicrobial and have even been attributed to fungal elements. Risk factors include obesity, diabetes mellitus, hypertension, chronic kidney disease, venous insufficiency, immunodeficiency, and alcohol and drug abuse [10]. Diabetes mellitus is the most significant comorbidity and is associated with increased rates of limb amputations [10]. One subset of necrotizing fasciitis seen mostly in people with diabetes is Fournier's gangrene, a life-threatening infection of the male genitalia.

Diagnosis

History and Physical Examination

The initial presentation resembles cellulitis and demonstrates localized erythema, edema, and pain. As the infection progresses, vesicles, bullae, necrosis, and crepitus may develop. Distinguishing necrotizing fasciitis from cellulitis may be difficult; however, disproportionate pain on examination and pain outside the margin of erythema may indicate a more extensive infection. Systemic manifestations such as fever, confusion, septic shock, and multiple organ failure result in a high mortality rate and necessitate urgency with evaluation and intervention.



Fig. 8 Necrotizing fasciitis of the lower extremity

Evaluation

While laboratory and radiographic investigation may assist in making the diagnosis, surgical exploration should not be delayed when clinical suspicion is high.

Treatment

Early surgical debridement and fasciotomy are critical and should be accompanied by empiric broad-spectrum intravenous antibiotic administration. Repeat surgical debridement is often necessary (Fig. 8).

Erythrasma

General Principles

Erythrasma is a bacterial rash of the skin's stratum corneum commonly affecting interdigital and intertriginous locations and often confused with fungal infections.

Epidemiology

Corynebacterium minutissimum is the causative organism [11]. Healthy adults, especially African Americans, are predominantly affected while patients who live in hot, humid climates, are obese, or have diabetes mellitus are more susceptible to infection.

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Diagnosis

History and Physical Examination

The eruption is characterized by a well-demarcated, hyperpigmented, and erythematous, macular patch with variable degrees of pruritus. Wood lamp examination exhibits a coral-red fluorescence and may aid in diagnosis.

Treatment

Topical therapy with clindamycin or erythromycin is effective in managing localized infections, while oral erythromycin or clarithromycin may be necessary for extensive disease. Recurrence is common, but the risk may be curtailed by the implementation of proper hygiene and weight loss lifestyle modification.

Viral Diseases of the Skin

Herpes Simplex

General Principles

Herpes simplex is a lifelong neurocutaneous disorder occurring secondary to viral pathogens that lay dormant in neurons until they episodically recur and manifest as mucocutaneous eruptions.

Epidemiology

Herpes simplex virus type 1 (HSV-1) is predominantly responsible for non-genital infections, although herpes simplex virus type 2 (HSV-2) can cause herpes labialis and other variations. The virus is acquired through direct contact and fomite transmission and is most often encountered through nonsexual contact in childhood. Adolescents and adults are often infected through kissing and sharing utensils and straws. There is a gender preference for females, and risk factors for infection include early sexual experiences, frequent and multiple sexual partners, history of a partner with oral lesions, and personal history of non-HSV sexually transmitted infections [12].

Diagnosis

History and Physical Examination

Oral HSV-1 is the most likely presentation to be encountered in the primary care setting. As with other herpetic infections, a prodrome of fever and malaise may precede the mucocutaneous eruption. Primary HSV-1 infection, also known as herpetic gingivostomatitis, is characterized by multiple vesicles on swollen erythematous bases distributed throughout the oral mucosa and lips and subsequently ulcerating into severely painful lesions. Regional lymphadenopathy is often observed. The course of this disease, through the complete resolution of all symptoms, may take up to 2 weeks.

Recurrent labial herpes is often heralded by sensations of paresthesias, itching, and burning at the location of the future eruption and is stimulated by illness, stress, trauma, and UV light exposure [12]. Clusters of painful vesicles appear on the lip's vermillion border, which then ulcerate and crust over followed by resolution in about 1 week. Recurrence rates differ between patients, with some never experiencing a herpetic flare. With subsequent manifestations, the symptoms are often less severe, and the clinical course is abbreviated.

Herpetic keratitis results from an ocular viral infection and must be treated urgently to avoid chronic scarring of the cornea and blindness [12]. Herpetic whitlow affects the hands and digits and is frequently acquired by children who suck their thumbs and bite their nails and healthcare workers who examine patients without proper personal protective equipment. Wrestlers may encounter herpes gladiatorum, which commonly appears on the torso after skin-to-skin contact. In patients with eczema, an HSV outbreak may superimpose itself over atopic areas resulting in a dermatologic emergency known as eczema herpeticum [12].

Evaluation

The diagnosis of herpes simplex can usually be made through a careful history and physical examination. In atypical presentations, or when the diagnosis is in question, viral cultures, PCR,

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serology, antibody testing, and Tzanck smears can be implemented to confirm suspected infection.

Treatment

Children with acute, primary herpetic gingivostomatitis can be managed effectively with oral acyclovir suspension. Systemic treatment with nucleoside analogs, such as acyclovir and valacyclovir, is indicated for recurrent herpes labialis outbreaks. Topical therapies can be applied; however, they are not as effective as oral preparations. In patients with numerous recurrences, prophylactic antivirals can be administered (Fig. 9).

Genital Herpes

General Principles

Genital herpes is a prevalent sexually transmitted infection characterized by recurrent, vesicular eruptions of the groin secondary to a lifelong, acquired viral infection.

Epidemiology

Genital herpes may be caused by HSV-1 and HSV-2 infections. Historically, groin outbreaks were predominantly attributed to HSV-2; however, changes in sexual practices have increased HSV-1 prevalence to half of all new cases acquired [13]. Risk factors for viral acquisition include black race, female sex, numerous and unsafe sex encounters, and the presence of other sexually transmitted infections. Also, individuals with HSV-2 have an increased risk of acquiring HIV.



Fig. 9 Herpes labialis on the lip's vermillion border

Diagnosis

History and Physical Examination

Outbreaks of genital herpes include single and clustered vesicles that ulcerate, causing pain, itching, and burning. Areas affected include the genitals, perineum, perianal areas, buttocks, and upper thighs, and associated lymphadenopathy may be present. Primary infections may be accompanied by malaise and fever, while subsequent outbreaks are generally less severe and are sometimes preceded by a prodrome. HSV-1 eruptions are often milder, and recurrences are less frequent than HSV-2 infection. Concurrent HIV-positive status increases the severity of HSV-2 flare-ups. Some patients remain asymptomatic carriers, and viral shedding may occur without active expression of the disease.

Evaluation

In patients with clinical disease, type-specific confirmatory testing is recommended to guide management and counseling. Active lesions should be analyzed by PCR, while asymptomatic patients with a history of outbreaks should be evaluated with serologic testing. Partners of HSV-infected patients should also receive type-specific serologic testing to assess their risk of HSV acquisition.

Treatment

Management of genital herpes may be episodic for acute eruptions, or suppressive to prevent recurrence or transmission. Nucleoside analogs such as acyclovir are all equally effective at decreasing the duration and severity of symptoms. Suppressive therapy can reduce the risk of HSV transmission to at-risk partners; however, in patients with HSV-2 and concurrent HIV, suppressive treatment is ineffective at reducing the spread of genital herpes [13].

In pregnant patients with genital herpes, suppressive therapy should be initiated from 36 weeks to term, and laboring women with active lesions should be offered elective cesarean delivery.

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Herpes Zoster

General Principles

Herpes zoster, or shingles, is the cutaneous manifestation of the reactivation of the dormant varicella virus inhabiting neurons of infected individuals. Zoster represents a pervasive syndrome, and its sequelae can result in chronic debilitation.

Epidemiology

Shingles occur secondary to varicella zoster, the same virus responsible for chickenpox and to which most American adults have been exposed. Reactivation of the dormant pathogen results in the characteristic eruption associated with zoster. With age, the risk of manifesting the disease increases significantly as the immune system naturally weakens, while immunosuppressive disorders such as HIV also confer susceptibility.

Diagnosis

History and Physical Examination

The classic shingles rash is often preceded by a prodrome of symptoms, including fever, malaise, and abnormal skin sensations such as itching and burning. The typical outbreak consists of maculopapular lesions confined to a single, unilateral dermatome which develop into clear, then cloudy, vesicles. Crusting eventually occurs, followed by rash resolution in 2–4 weeks. Scarring and pigmentation changes may develop, and nerve injury secondary to inflammation can result in a chronic pain syndrome known as postherpetic neuralgia. Most rashes are distributed along the dermatomes between T1 and L2; however, viral reactivation in the fifth cranial nerve can result in a condition known as zoster ophthalmicus [14].

Evaluation

In most cases, the diagnosis can be made clinically; however, PCR analysis of vesicular fluid can be utilized for atypical presentations or when the diagnosis is in question.

Treatment

Acyclovir, famciclovir, and valacyclovir decrease the duration of symptoms and pain severity, especially if initiated within 72 h of the eruption. Adjunctive glucocorticoids may help with discomfort and inflammation; however, they do not decrease the incidence of postherpetic neuralgia, as previously recorded. Acetaminophen and nonsteroidal anti-inflammatories are recommended for the management of mild to moderate symptoms. Postherpetic neuralgia may be treated topically with lidocaine patches or capsaicin cream and systemically utilizing anticonvulsants, tricyclic antidepressants, and, in severe cases, opioids [14].



Fig. 10 Herpes zoster of the trunk

For herpes zoster prevention, the Advisory Committee on Immunization Practices recommends the use of the recombinant zoster vaccine known as Shingrix beginning at age 50. Two doses of Shingrix are delivered 2–6 months apart and are encouraged even if its predecessor, Zostavax, was previously administered [15] (Figs. 10 and 11).

Viral Warts

General Principles

Warts are benign neoplasms resulting from a viral infection of the skin's epidermal layer.

Epidemiology

Viral warts arise secondary to human papillomavirus. Many different subtypes of this virus exist and manifest with unique presentation and at different locations of the body. In general, cutaneous

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Fig. 11 Zoster ophthalmicus

warts occur most commonly in childhood, while mucosal and genital warts arise in sexually active adolescents and adults, most often in women. Risk factors for epidermal warts include immunosuppression, contact with infected individuals, nail-biting, and walking barefoot.

Diagnosis

History and Physical Examination

Warts present as hyperkeratotic papules and plaques with pathognomonic thrombosed capillaries appearing as small, black dots. Verruca vulgaris appear most commonly on the hands with periungual variations developing adjacent to nails. Plantar warts sprout near pressure points on the soles of the feet and may exhibit discomfort. Planar warts, occurring most often on the face, can be more challenging to diagnose due to their flat appearance and lack of characteristic thrombosed vessels [16]. Sexually transmitted, condylomatous warts erupt on the skin and mucous membranes of the genitalia and anus and, if left untreated, may develop into large, cauliflower-like vegetations known as condyloma acuminatum.

Treatment

Most warts will resolve spontaneously; however, they can cause discomfort and cosmetic concern, and some cases are recurrent or recalcitrant to therapy. Several different treatment modalities exist, none of which has good evidence for consistent effectiveness or superiority to one another. Topical application of salicylic acid and cryotherapy are management options often implemented in primary care settings. Imiquimod is frequently utilized for condylomatous warts and may be used as second-line therapy for recalcitrant cutaneous warts. Laser ablation, photodynamic therapy, immunomodulation with injected candida antigen, and surgical removal are all emerging treatment options that may be available in secondary care settings [16] (Figs. 12 and 13).

Molluscum Contagiosum

General Principles

Molluscum contagiosum is a highly transmissible viral infection of the skin's keratinocytes spread by direct patient contact, indirect fomite exposure, or autoinoculation through scratching.

Epidemiology

The poxvirus molluscum contagiosum virus is responsible for the epidermal lesions. Children are most commonly infected; however, sexually active adults and immunocompromised individuals may also develop symptoms. The characteristic rash generally appears 2–6 weeks after viral exposure and may persist for months to years.

Diagnosis

History and Physical Examination

Flesh and pink-colored, pearly, dome-shaped papules with central umbilication appear and range in size from 1 mm to 1 cm in diameter. Common eruption locations include the face, trunk, limbs, and axilla and spare only the palms and soles. The anogenital region, abdomen, and thighs are more frequently subject to an outbreak in sexually transmitted infections. Erythema and inflammation may develop as part of the normal immune response or may indicate a secondary bacterial infection.

Treatment

Because the lesions resolve spontaneously, the treatment of non-irritating molluscum is unnecessary. Removing children from school or daycare is

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Fig. 12 Viral wart of the index finger



Fig. 13 Plantar warts

also not warranted [17]. If treatment is desired for cosmetic or other reasons, several in-office modalities exist. Topical cantharidin application, curettage, and liquid nitrogen cryotherapy are all appropriate management options. Scratching avoidance, proper hygiene practices, and safe sex in adults may all prevent molluscum transmission (Fig. 14).

Fungal Infections of the Skin

Dermatophytoses

General Principles

Tinea disorders are a group of cutaneous infections caused by dermatophytes, fungal organisms that affect keratinized structures such as the skins' stratum corneum, hair, and nails.

Epidemiology

Trichophyton rubrum is the most common causative fungal species in humans; however, several different dermatophytes can result in infection. Tinea corporis and tinea capitis, which occur on the body and scalp, respectively, mainly occur in prepubescent children. Tinea cruris results in a groin outbreak and almost exclusively develops in males. Tinea pedis, an interdigital foot manifestation, is commonly known as "athlete's foot" and occurs in patients who walk barefoot in communal areas and have persistently sweaty feet. Both tinea cruris and tinea pedis are most frequently found in adolescents and young adults and often occur concurrently. Tinea manuum, an eruption on the hand, can be secondary to autoinfection from scratching an affected foot and is commonly referred to as two feet-one hand syndrome. Dermatophytes may also affect facial hair in adult males, a diagnosis known as tinea barbae. In wrestlers, a version called tinea gladiatorum occurs. Tinea conditions are more common in warmer climates, and individuals with excessive perspiration, diabetes mellitus, and immunocompromise and who wear occlusive garments are predisposed to infection.

Diagnosis

History and Physical Examination

Tinea, in all its forms, generally appears as a pruritic, erythematous, scaling, annular rash with central clearing and an advancing border. The lesions may be isolated or may confluence into a more diffuse eruption. Tinea capitis is associated with localized alopecia. If left untreated, scalp infections may progress to a boggy and indurated inflammatory condition known as a kerion. Tinea cruris infects the skin of the thighs opposite the scrotum but spares the actual genitalia. This feature, as well as a lack of satellite lesions, can help differentiate tinea cruris from candida intertrigo. Tinea pedis classically affects the toe webs; however, it can spread to the plantar and lateral aspects of the foot, commonly referred to as a "moccasin pattern" [18].

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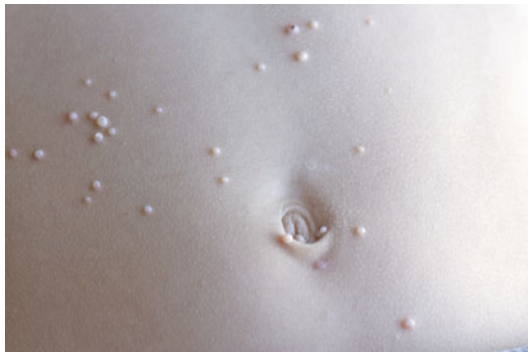


Fig. 14 Molluscum contagiosum of the abdomen

Evaluation

The diagnosis of tinea can often be made clinically by observing the characteristic rash; however, microscopy using potassium hydroxide (KOH) preparations can aid when the diagnosis is in question. While Wood lamp examination can demonstrate fluorescence with some dermatophyte infections, its uses are limited and false negatives may occur if the area viewed has recently been washed. Knowledge of erythrasma's coral-red fluorescence by Wood lamp can help exclude this bacterial infection from the differential when investigating possible dermatophyte rashes. Histology using periodic acid-Schiff (PAS) stains can be performed but is rarely indicated.

Treatment

For localized infection, topical azoles, such as ketoconazole, or allylamines, such as terbinafine, are effective. For severe, diffuse, or recalcitrant cases, oral preparations of antifungals such as terbinafine or itraconazole can be implemented. Oral ketoconazole is no longer recommended due to hepatotoxicity. Tinea capitis must be managed with systemic antifungals with griseofulvin commonly used in children and azoles and allylamines used in adults. Sporicidal shampoos may be used as adjunctive management of tinea capitis. Nystatin is used for candida infections and is not effective against dermatophytes. Topical steroids are currently categorized as a mistreatment for tinea infections. They may initially help with pruritus and inflammation; however, the rash will recur, or its characteristic appearance will be obscured in a condition known as tinea incognito.

Prevention can be achieved by improved hygiene, non-occlusive clothing, and removal of moist garments after perspiration (Figs. 15 and 16).

Onychomycosis

General Principles

Onychomycosis is a prevalent fungal infection affecting the nails of the hands and, more commonly, the feet.

Epidemiology

Trichophyton rubrum and other dermatophytes cause a majority of onychomycosis cases; however, non-dermatophyte molds and yeast are increasingly implicated in nail infections. Old age, obesity, and tinea pedis increase the risk for onychomycosis, while conditions such as diabetes mellitus and psoriasis predispose patients to infection [19].

Diagnosis

History and Physical Examination

Discoloration and thickening of the nail plate are the classic findings on physical examination and can progress to nail distortion and discomfort in advanced disease.

Evaluation

Microscopy using KOH, fungal cultures, histologic evaluation with PAS staining, and PCR are all available to confirm the diagnosis.

Treatment

Multiple treatment modalities are implemented in the management of onychomycosis. Protracted courses of oral antifungals such as terbinafine are often prescribed, and newer topical preparations such as efinaconazole are demonstrating

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Fig. 15 Tinea corporis



Fig. 16 Tinea pedis

improved efficacy. Traditionally, due to the cost and adverse events associated with systemic treatments, confirmatory testing has been recommended before initiation of oral treatments. New studies suggest that empiric therapy with terbinafine, without organism verification by KOH, may be preferred as the cost of terbinafine is minimal, and hepatotoxicity is less significant than previously speculated [20]. Some guidelines still suggest confirmatory testing. Also, following baseline liver function tests before initiating terbinafine, subsequent laboratory monitoring may not be necessary unless symptoms arise or a history of liver dysfunction is present. Due to the high cost of newer topical therapeutics, the diagnosis should be confirmed with PAS histology before their initiation. Nail debridement may also be implemented to improve cure rates (Fig. 17).



Fig. 17 Onychomycosis of the toenails

Yeast

General Principles

Candidiasis, or yeast infections, represent a group of non-dermatophyte fungal eruptions that affect the epithelium of cutaneous and mucosal surfaces.

Epidemiology

Yeast infections are overwhelmingly caused by *Candida albicans* with other candida species also causing pathology. Candida intertrigo is the most common cutaneous manifestation and affects the moist and friction-laden skin of intertriginous locations. A variation known as candida diaper dermatitis affects the groin and buttocks of newborns and infants. Thrush is an oral, mucocutaneous disorder affecting newborns and at-risk adult hosts. Candidal vulvovaginitis and candida balanitis are yeast infections of the female and male sexual organs, respectively. Obesity, excessive perspiration, diabetes mellitus, frequent steroid or antibiotic use, and any condition that compromises immune functioning place patients at increased risk for yeast infections [21].

Diagnosis

History and Physical Examination

The cutaneous candida rash is characterized by a pruritic, erythematous, finely scaling eruption with associated satellite lesions that occur in

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intertriginous areas such as the axillae, groin, inframammary and sub-pannus regions. Infants commonly present with a diaper dermatitis variant of this condition, which may feature maceration and fissures. Thrush is defined by white plaques adherent to the tongue and oral mucosa, which, when removed, reveal erythematous epithelium. In females, itching, burning, and dysuria are accompanied by a white, curdy discharge and erythematous, tender vaginal mucosa in the vulvovaginal manifestation of candida infections. Uncircumcised men are at increased risk for balanitis, which causes tender, erythematous inflammation of the glans and shaft of the penis [2].

Evaluation

Diagnosis is mainly clinical; however, KOH-aided microscopy of the skin and tongue and vaginal wet preps can be implemented if other conditions cannot be excluded by the history and physical examination alone. Budding yeast and septate hyphae are positive findings visualized on microscopy.

Treatment

Management of most cutaneous yeast infections can be accomplished with the application of a topical antifungal such as nystatin or one of the topical azole preparations. Thrush can be eradicated by nystatin oral suspension, and some adults may require systemic treatment with fluconazole. Uncomplicated vulvovaginal candidiasis can be treated with a single dose of oral fluconazole or a number of azole intravaginal creams. Severe, recurrent, and recalcitrant cases of vaginal yeast infections may require multiple doses of fluconazole over an established treatment duration. Therapies for balanitis are similar to those for vulvovaginal disease [2]. Steroid creams and ointments may help initially with discomfort and inflammation; however, they should not be utilized as they can prolong the course of infection.

Medication review, as well as lifestyle modification, including weight loss, avoidance of excessive perspiration and occlusive garments, and frequent diaper changes, may prevent future candida outbreaks (Fig. 18).



Fig. 18 Oral candidiasis (thrush)

Tinea Versicolor

General Principles

Tinea versicolor, or pityriasis versicolor, is a common fungal infection of the torso and proximal extremities, which is named for the variable pigmentation presentations that appear based on the patient's complexion and skin tone.

Epidemiology

Tinea versicolor is caused by *Malassezia*, a fungal component of healthy skin flora, which becomes pathogenic in patients who live in hot and humid conditions, have oily skin, are immunodeficient, or who have a genetic predisposition. Adolescents and young adults are primarily affected due to the hospitable environment provided by their skin's increased sebum production. Pityriasis versicolor has no gender or racial predominance [22].

Diagnosis

History and Physical Examination

As the name implies, tinea versicolor is characterized by numerous, scaling ovals of varied pigmentation. The typical distribution involves the neck, trunk, and extremities with single well-defined lesions that confluence into larger patches and plaques. The eruption may be erythematous to

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hyperpigmented in lighter complexions and hypopigmented in darker-skinned patients. Light pruritus may occur, but most presentations are asymptomatic.

Evaluation

The diagnosis can be made clinically; however, Wood lamp fluorescence and KOH preparations may be utilized when the diagnosis is unclear. The spores and hyphae visualized on microscopy have been traditionally described as "spaghetti and meatballs."

Treatment

Topical antifungals such as ketoconazole are the preferred first-line treatments, and other over-the-counter preparations such as selenium sulfide may also be implemented topically. Oral antifungals can be used as second-line agents in severe, recurrent, and recalcitrant cases; however, systemic ketoconazole is no longer recommended due to hepatotoxicity (Figs. 19 and 20).



Fig. 19 Tinea versicolor of the trunk and upper extremities

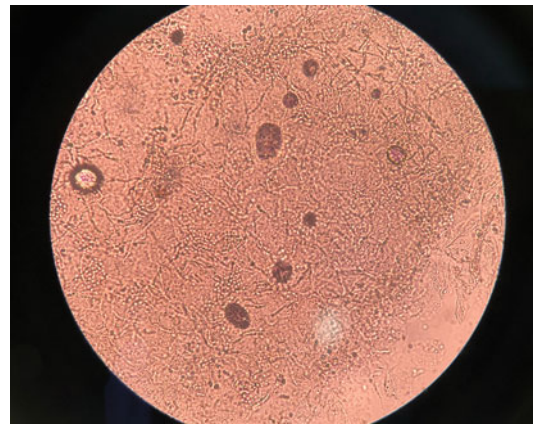


Fig. 20 Spores and hyphae visualized on microscopy of tinea versicolor skin scrapings "spaghetti and meatballs"

Infestations

Lice/Pediculosis

General Principles

Pediculosis is an obligate blood ectoparasite infestation resulting in symptoms of intense pruritus. This misunderstood condition provokes anxiety for patients, parents, and school healthcare personnel, leading to an often undue burden for those involved.

Epidemiology

Pediculus humanus capitis, *Pediculus humanus corporis*, and *Pthirus pubis* affect the scalp, body, and pubic region, respectively. Transmission is less pervasive than is commonly perceived and requires direct, close contact due to the louse's inability to jump or fly. Pediculosis capitis is often observed in school-aged children, while pediculosis corporis should be suspected in individuals with poor hygiene or who live in crowded conditions. Pediculosis pubis is found in sexually active adolescents and adults.

Diagnosis

History and Physical Examination

The diagnosis of pediculosis requires direct visualization of at least one live louse and can be aided by a lighted magnifying lens and a fine-toothed nit comb. Observation of nits alone does not indicate an active infestation and does not warrant intervention. Body lice are often found in the seams of clothing upon examination [23]. Family members should be examined if the diagnosis is confirmed.

Treatment

The insecticidal agent permethrin is the preferred first-line agent for the management of pediculosis. As with other non-ovicidal treatment options, permethrin should be administered on two occasions

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7–10 days apart. Non-insecticidal preparations are available such as benzyl alcohol 5% lotion and dimethicone solution and may be used as second-line therapeutics in some populations [23]. Ovicidal agents such as malathion, spinosad, and ivermectin may be used in refractory cases or in areas where resistance to permethrin is documented [23]. Malathion is restricted in children under 6 years of age, and lindane should no longer be used due to neurotoxicity in humans.

Wet combing is a nonpharmacologic management option often implemented by patients wanting to avoid adverse events from chemical exposure. This intervention is time-consuming and has variable success rates.

Pediculosis pubis should be managed with permethrin 1%, with malathion 0.5% lotion, or oral ivermectin as second-line therapies [23]. Patients with pubic lice should be screened for sexually transmitted infections, and sex partners from the last month should be treated [23]. Recommendations for pediculosis corporis include hot-water washing clothing and bedding and an increased emphasis on personal hygiene.

A "no-nit" policy for schools and daycares is not recommended as only live lice indicate an active infestation. Because the likelihood of transmission is low, children should not be removed from school during treatment, even when an active infestation is present (Figs. 21 and 22).

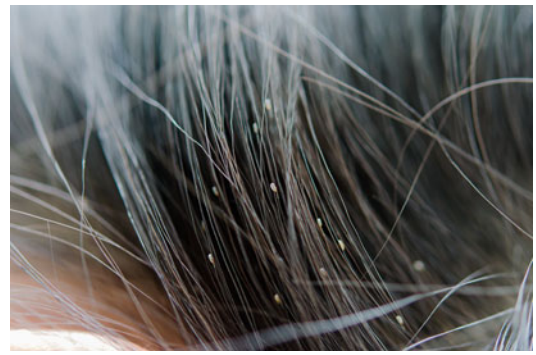


Fig. 21 Nits attached to the hairs of a patient with pediculosis humanus capitis



Fig. 22 Louse visualized on microscopy

Scabies

General Principles

Scabies is a common mite infestation transmitted to patients via skin-to-skin or fomite contact. The resulting dermatitis is intensely pruritic and follows a characteristic body distribution. Because scabies is often misdiagnosed, careful attention to history, physical examination, and diagnostic methods must be considered for prompt and accurate identification.

Epidemiology

The fertilized female *Sarcoptes scabiei* mite burrows through the stratum corneum, releasing eggs and fecal material. The larvae hatch and emerge to the skin's surface to mate and repeat the cycle. The typical severely pruritic eruption is preceded by mild symptoms while the body develops a hypersensitivity reaction to the mite products. This initial delay can take up to 6 weeks and may confuse an already tricky diagnosis [23]. Individuals living in overcrowded conditions, and those with poor hygiene or nutritional status, are at increased risk for infestation.

Diagnosis

History and Physical Examination

Erythematous papules, pustules, vesicles, and nodules occur most commonly on the hands, wrists, axilla, waistline, buttocks, and genitalia. The face and neck are spared in adults; however, infants may present with lesions on these areas as

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Fig. 23 Hand with scabies dermatitis

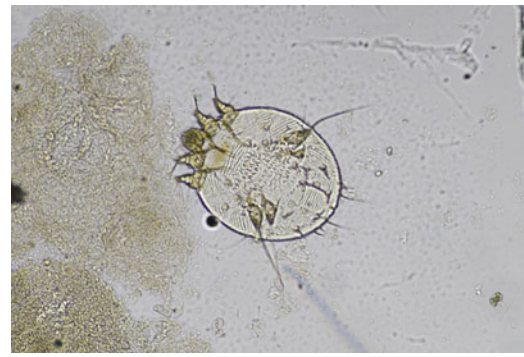


Fig. 24 *Sarcoptes scabiei* mite visualized on microscopy

well as the palms and soles. The pathognomonic burrows of webs and creases are not always apparent.

Evaluation

Microscopy of skin scrapings is used to identify mites, eggs, and fecal particles diagnostic for scabies infestation. Dermoscopy is increasingly being utilized in the evaluation of scabies [23].

Treatment

Topical permethrin cream is the first-line therapy and should be applied from the neck down. The application should remain overnight or at least 8 h and should be repeated in 1 week. Oral Ivermectin is another treatment option; however, it should only be prescribed for patients who have failed an appropriate course of topical permethrin. Patient education is critical in the management of scabies. Bedding and clothing should be washed at a temperature of at least 122°F (50°C) and hot, machine dried [23]. Close contacts should be identified, and recent sex partners should be treated. Individuals should be informed that symptoms may persist up to 2 weeks after successful treatment (Figs. 23 and 24).

Chiggers

General Principles

Trombiculosis or "chiggers" is the infestation of human skin by the Trombiculidae mite larva resulting in a pruritic rash of the groin and ankles [24].

Epidemiology

The *Trombicula* mites, also known as the harvest mites, progress to their larval stage on blades of grass where they attach to human skin and migrate to areas where they are hindered by constrictive clothing such as the ankles and waistline. In the northern United States, chiggers occur in the spring and summer months, while the warmer climate of the south sponsors the harvest mite year-round [24].

Diagnosis

History and Physical Examination

A pruritic eruption of clustered papules and pustules occurs in the typical distribution of the ankles, legs, and waistline. Symptoms are self-limited and resolve within 72 h; however, a hypersensitivity reaction may lead to prolonged edema and urticaria [24].

Treatment

Prevention with DEET-containing insect repellants applied to the skin and garments is effective. Symptomatic treatment of pruritus can be achieved with antihistamines and topical steroids.

Bedbugs

General Principles

The downward trend in bedbug incidence in the twentieth century has reversed over the last two

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decades with a resurgence in infestations secondary to pesticide resistance, frequent travel, lack of public education, and ineffective pest control programs [25]. Contrary to general perceptions, these obligate blood parasites are responsible for a significant burden on patients, including substantial psychological distress and financial strain.

Epidemiology

The light-aversive insects belonging to the family Cimicidae remain hidden within the proximity of its host's sleeping area. They are drawn to the warmth and carbon dioxide produced by humans, inconspicuously feeding, thanks to the anesthetic properties of their saliva [25]. The components of this saliva are responsible for the host reaction and subsequent dermatitis. Increased population density and high resident turnover rates increase the risk of infestation. The false assertion that poor hygiene contributes to patient susceptibility bolsters the stigma associated with bedbugs [25].

Diagnosis

History and Physical Examination

The cutaneous manifestations of a bedbug infestation are varied, which can lead to diagnostic difficulty and a broad differential. A pruritic, erythematous, maculopapular rash affecting unclothed areas is typical; however, patients may also present with papules, vesicles, and wheals. Linear rows of bites referred to as "breakfast, lunch, and dinner" have been classically associated with bedbug dermatitis. Secondary bacterial infections can occur from the excoriation of the intensely pruritic bites.

Treatment

The cutaneous reaction to bedbugs is self-limited and usually resolves within 1–2 weeks. No intervention has demonstrated efficacy at altering the natural history of bedbug eruptions; however, topical steroids and antihistamines can manage pruritus, while topical antibiotics can treat secondary bacterial infections.

The Environmental Protection Agency (EPA) and the Centers for Disease Control and Prevention (CDC) endorse a comprehensive, integrated pest management strategy for addressing site infestation [25]. Multiple pest eradication modalities should be implemented under the supervision of professional exterminators. Due to bedbugs' resistance to temperature extremes, non-washable items should be treated at 120 °F (48.9 °C) or hotter for at least 2 h or 23 °F (−5 °C) or colder for 5 days [25] (Fig. 25).



Fig. 25 Bedbug infestation of a bed frame

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Skin Tumors

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Elisabeth L. Backer

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General Principles

While the current US Preventive Services Task guidelines [1] may not promote routine screening, children, adolescents, and young adults who have fair skin should be counseled about limiting their exposure to ultraviolet (UV) radiation in order to reduce the development of skin cancer. Attention should be paid to examining the skin during regular physical examinations, in addition to evaluating lesions that are concerning to patients or have undergone changes of any kind.

Risk factors for skin cancer include light skin, sunny or high-altitude climates, prior sunburns, atypical nevi, prior history of skin cancer, and a family history of skin cancer as well as exposure to radiation. Those older than 65 years of age are at greater risk for cancerous skin tumors such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma.

Approach to the Patient

History

It is important to ascertain the duration of the onset of a skin tumor, as well as its associated symptoms such as pain, pruritus, and possibly paresthesias. While some skin growths can be linked to acute illnesses, others may have a connection to chronic symptoms including fatigue, weight loss, and malaise – thus a review of systems would be helpful. Other associated factors that may need to be explored include the patient's vocation and hobbies, travel history, sun exposure, prior skin cancers, and prior skin treatments.

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Physical Examination

Once the patient's overall condition and general health have been assessed, the skin tumor itself can be evaluated based on type of growth (such as nodule, cyst, papule, or scar), the color of the lesion (such as red in erythroplakia, or black in melanoma), the shape of the tumor (such as dome shaped in keratoacanthoma, or irregular in melanoma), and the texture of the growth itself (such as soft in lipoma and rough in actinic keratosis). Vascular characteristics should also be noted, often heralding neovascularization of cancerous growths. Sun damage and scarring should also be assessed. Dermoscopy aids in magnification of lesions – and by distinguishing between benign and suspicious lesions, can decrease unnecessary biopsies.

The final diagnosis of a skin lesion is frequently determined by biopsy and the resulting histopathology. A referral to a dermatologist may be in order for lesions that are not clearly benign, those that are suspicious of malignancy or those requiring specific treatment or cosmetic outcomes.

Keratosis

Seborrheic Keratosis (SK)

See (Fig. 1).

General Principles

Definition

SKs are very common pigmented benign skin tumors, occurring mainly on the torso and face, consisting of mature keratinocytes. They form as epidermal cells and undergo localized proliferation – and generally occur after age 30–50. Certain cases are linked to a genetic predisposition. When SKs arise more numerously and more rapidly, it can be a sign of underlying disease, such as a GI tract malignancy or lung cancer (Leser-Trelat sign).

Epidemiology

SKs can be somewhat more common and more plentiful in men. The incidence tends to increase with advancing age.

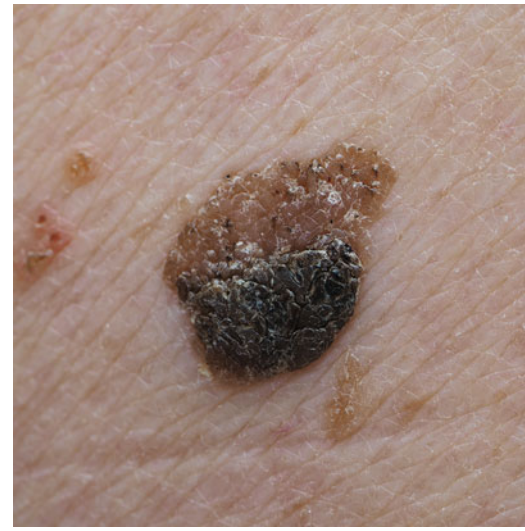


Fig. 1 Seborrheic keratosis. (Image provided by Dept of Dermatology, UNMC)

Classification

Common SKs – also known as basal cell papilloma or solid seborrheic keratosis

Reticulated SKs – also known as adenoid seborrheic keratosis

Inflamed SKs – associated redness and irritation

Diagnosis

History

Patients will usually describe a discolored, slow growing skin lesion (expanding over months to years) that is not associated with any pruritis or tenderness. Some patients attempt to remove the lesion through scratching. When exposed to friction, these lesions can become inflamed or irritated – and can show signs of bleeding [2].

Physical Examination

SKs are round to oval and can vary in size from a few millimeters to several centimeters in diameter. Their typical appearance is that of a "stuck on" lesion, which feels waxy or rough to touch. Color variations range from tan, to light brown, to dark brown and almost black. When inflammation is present, SKs look reddish in color. Under magnification of a dermoscope, the surface shows keratin cysts and comedo-like openings.

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Special Testing
When SKs appear atypical or inflamed, a biopsy or removal of the lesion may be warranted.

Differential Diagnosis
SKs need to be differentiated from pigmented BCCs, malignant melanoma, SCCs, solar lentigos, acrochordons, verrucae vulgaris, nevi, and actinic keratoses.

Treatment
No specific treatment is needed for most SKs. Cryotherapy, light electrocautery, or shave biopsy can be utilized if lesions are to be removed [3]. Most patients prefer cryotherapy as no specific wound care is required.

Referrals
Patients with extensive lesions may benefit from a dermatology referral.

Counseling
Treatment of SKs may result in scarring and post-inflammatory hyper- or hypopigmentation.

Patient Education
Patients can be reassured regarding the benign nature of SKs; they do however tend to increase in number with age and can be a cosmetic concern.

Actinic Keratosis (AK) or Solar Keratosis

General Principles

Definition
AKs present as single or multiple scaly lesions on sun-exposed areas of fair-skinned individuals. They occur on a continuum with SCC, and while most AKs do not progress to SCC, 60% of SCC arise out of preexisting AKs. AKs are linked to chronic ultraviolet (UV) radiation exposure and are made up of atypical keratinocytes.

Epidemiology
AKs represent the most common reason for dermatology visits. They usually occur in middle-aged men and are often found in older adults. In areas of high sun concentration such as the Southwestern US or Australia, they may occur at a younger age. Certain skin types are especially susceptible, as are outdoor workers and outdoor enthusiasts. Immunosuppressed patients and those with organ transplants are at a heightened risk for AKs and SCC.

Approach to Patient

Diagnosis

History
Patients will report having noticed an erythematous, scaly lesion over months to years. At times AKs can feel sensitive to touch or be slightly pruritic.

Physical Examination
AKs are typically diagnosed by inspection as well as touch. The lesions can appear reddish, yellow-brown, or skin-colored, while their surface feels rough or sandpapery. Their size varies between 3 and 10 mm. They can occur as isolated or scattered lesions and are commonly located on the face, ears, neck (thinner lesions) and on the forearms, hands, and legs (thicker lesions). Clinical variations include classic, hypertrophic, atrophic, and pigmented AKs, as well as actinic cheilitis and those with a horn.

Special Testing
A deep shave or punch biopsy is advised when SCC is suspected or when lesions appear atypical, including those that have grown rapidly, are tender or ulcerated, or those that fail to respond to treatment

Differential Diagnosis
AKs need to be differentiated from SCC, BCC, inflamed seborrheic keratosis, eczema, and discoid lupus erythematosus and porokeratosis.

Treatment
Since AKs can lead to the development of SCC, treatment is usually recommended. When multiple lesions are present, topical medication may be preferred. Cryotherapy is effective for the majority of lesions: thinner lesions can be treated for 5–10 s,

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whereas thicker lesions may need >10 s or repeat applications. Two freeze-thaw cycles are typically used.

Medications
Local twice daily application of 5% 5-fluorouracil for days to even weeks can be effective, but can cause skin irritation. Topical imiquimod 5% cream can also be considered, but may be less effective. Chemical peels as well as photodynamic therapy are very effective. The latter is used in conjunction with a skin sensitizing agent.

Referrals
In patients with extensive or atypical lesions, a dermatology referral may be appropriate.

Counseling
Patients should be warned that topical agents such as 5-FU or imiquimod can lead to significant skin irritation. Cryotherapy can result in areas of hypopigmentation and scarring.

Patient Education/Prevention
Skin monitoring for new or recurring lesions is advised. Sun protection and broad-spectrum sunscreen is advised. Patients should avoid the sun during the peak hours in the spring and summer [4].

Pigmented Lesions

Nevus (Mole)

General Principles

Definition
Melanocytic nevi are pigmented macules or papules. They consist of groups of melanocytes which can be found in the epidermis, dermis, or subcutaneous tissue. Nevi can be classified by history as acquired [5] or congenital melanocytic nevi. Acquired melanocytic nevi can be divided by histopathology as junctional, dermal, and compound nevi. Other variants include atypical, blue, halo, or Spitz nevi. Dermoscopy [6] allows for further detailed categorization based on the amount and distribution of pigmentation.

Epidemiology
Nevi are commonly seen in Caucasians. They are acquired during childhood into adulthood, with most adults having about 20 nevi. Nevi that arise de novo in older adulthood may need to be evaluated.

Types of Nevi

Junctional Nevus
This nevus presents as tan to dark brown macule with smooth, round borders – and is found at the dermo-epidermal junction.

Dermal Nevus
This nevus is situated exclusively in the dermis, does not produce melanin, and is therefore usually skin colored.

Compound Nevus
This nevus has elements of both a junctional and a dermal nevus, is tan to dark brown in color, and presents as pigmented papule with a smooth or papillomatous surface.

Atypical Nevus
This nevus has atypical and irregular features to it, given the uneven distribution of melanocytes, thereby having some clinical similarity to melanoma [7]. Atypical nevi have also been called dysplastic nevi. The prevalence of atypical nevi is 2–8% in Caucasians. FAMM is a familial syndrome marked by multiple and atypical moles and the presence of melanoma in first- or second-degree relatives. This syndrome increases the risk of developing melanoma.

Blue Nevus
This nevus presents as a firm, blue to gray-black papule to nodule, and arises out of melanin-producing dermal melanocytes. It occurs in late adolescence.

Halo Nevus
Also known as Sutton's nevus, this nevus has an area of hypopigmentation surrounding the nevus itself. The decrease in melanin which gives rise to the halo is termed "leukoderma" and is based on

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an inflammatory response. Halo nevi are found on the chest, abdomen, and back, occurring in 1–5% of Caucasian children. Spontaneous regression of the nevus is seen over time.

Spitz Nevus

This nevus is typically found in childhood and presents as a red, hairless papule, usually <1 cm in size. When found in adulthood, melanoma may need to be excluded.

Congenital Nevus

Unlike acquired nevi, this nevus can be sizable and is present at birth; it has an increased risk of developing into melanoma especially when it is large or irregular.

Approach to Patient

Diagnosis

History

Patients may report noticing a new mole or changes within an existing mole. It is vital to obtain a personal history with respect to sun exposure and a family history regarding melanoma.

Most lesions occur during the younger years into adulthood, and are asymptomatic. Those that are pruritic or tender may point to underlying malignant changes. Involution of lesions can occur by age 60.

Physical Examination

Nevi can present as flesh-colored, tan, pink, brown, blue, or gray-black lesions. A complete skin exam is key to identifying new or changing nevi, or those that have unusual characteristics (the "ugly duckling" sign [8]). Melanocytic nevi with atypical features [7] need to be differentiated from melanoma. The ABCDE description is commonly utilized [9]:

A: Asymmetry
B: Border irregularity
C: Color variation
D: Diameter greater than 5 mm.
E: Evolution (changes in shape, color or size of lesion)

Dermoscopy [6] aids the further evaluation of nevi through magnification and assists with distinguishing nevi from melanomas. Whereas nevi are symmetrical in appearance with a regular pigment network, melanomatous lesions are often asymmetrical, have blue or white coloring and an irregular pigment network when seen through a dermoscope. Two or more of the latter three features should prompt a biopsy.

Special Testing

Any atypical or suspicious or symptomatic nevus may need to be biopsied. An excisional full thickness biopsy is advised when melanoma needs to be excluded.

Differential Diagnosis

BCC, dermatofibroma, seborrheic keratosis, traumatic tattoo, and solar lentigo.

Treatment

Most benign appearing nevi can be observed over time. If a mole becomes symptomatic, it may need to be removed. Thin or protruding dermal nevi can be removed via shave biopsy. A punch biopsy is useful for smaller lesions that are less than 5 mm in diameter.

Behavioral

Medications

No specific medication is indicated for nevi.

Referrals

Large, very atypical, or multiple dysplastic appearing nevi may warrant a dermatology referral.

Counseling

Removal of lesions may lead to scarring, keloid formation, or hypopigmentation.

Patient Education

As described below, patients should be counseled to report any changes to their moles. Symptomatic lesions or those that bleed, and should be further evaluated as well.

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Prevention

As a general guideline, sun protections should be advised. Patients with multiple acquired melanocytic nevi should pursue periodic total body skin examinations.

Solar Lentigo or Actinic Lentigo

See (Fig. 2).

General Principles

Definition

Solar lentigos, commonly known as "liver spots" or "old age spots," are 1–3 cm pigmented epidermal macules, arising out of proliferation of normal melanocytes and keratocytes from chronic sun exposure [10]. The face, neck, back, shoulders, and extremities are usually affected. While these are benign lesions, they can undergo malignant transformation to form lentigo maligna melanoma.

Epidemiology

These lesions usually occur equally in men and women. They most often present in middle-aged Caucasians or Asians, but can occur at an earlier age in sunny climates.



Fig. 2 Solar lentigo. (Image provided by Dept of Dermatology, UNMC)

Classification

Solar lentigo: Most common lentigo, appearing brown and flat. Lesions can enlarge to 3–4 cm.

Pigmented solar lentigo: Also called spreading actinic keratosis, this solar lentigo looks like a seborrheic keratosis.

Lentigo maligna: This lentigo is also flat, but has distinct color variations including black flecks, and heralds transformation into a superficial spreading melanoma or melanoma in situ.

Peutz-Jeghers Syndrome: Multiple lentigos are seen on mucus membranes. This syndrome also features intestinal polyps.

Approach to Patient

Diagnosis

History

Patients report brown spots or macules on sun-exposed areas. These lesions multiply with age and turn darker in the summer and lighter in the winter months.

Physical Examination

Solar lentigos present as tan to brown/black flat macules. They can range from a few mm to 2–4 cm in size. The forehead, cheeks, nose, lips, hands, and forearms are most often affected, as they represent sun-exposed areas, but these lesions can also be seen on the back and chest. When dermoscopy is used, abnormal pigment distribution may herald a developing malignancy.

Special Testing

When a lesion is suspicious, a wide elliptical excision may be best. A punch biopsy can be useful when the lesion develops an area of rapid change.

Differential Diagnosis

Seborrheic keratosis, nevi, lentigo maligna melanoma, pigmented actinic keratosis.

Treatment

Observation may suffice. Smaller unsightly lesions can be treated with cryotherapy for as little

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as 5 s. If lentigo maligna is suspected, these lesions should be biopsied.

Medications

If lightening of these lesions is desired, hydroquinone 4% cream can be applied bid for several weeks. A triple combination cream made up of fluocinolone 0.01%, hydroquinone 4%, and tretinoin 0.05% is also available. Chemical peels or use of azelaic acid 20% cream bid for 2–4 weeks has been effective. Pigmented solar lentigos also respond to topical fluorouracil application for up to 10 days.

Referrals

Larger lesions or those appearing very atypical or undergoing rapid changes would benefit from a dermatology consult.

Counseling

Treatments can lead to hypopigmentation, localized irritation, and at times uneven bleaching.

Patient Education/Prevention

Any changing or symptomatic lesions should be further evaluated. Sun protection is advised to limit the formation of solar lentigos.

Malignant Skin Tumors

Melanoma

See (Fig. 3).

General Principles

Definition

Melanomas represent the most serious type of skin cancer. They are characterized by the irregular growth and expansion of abnormal melanocytes, spreading locally through lymphatic and systemically by hematogenous routes. Most melanomas are confined to the epidermis; infiltration of the dermis can lead to metastases. Whereas they can arise out of existing nevi, the majority (70%) of melanomas arise de novo.

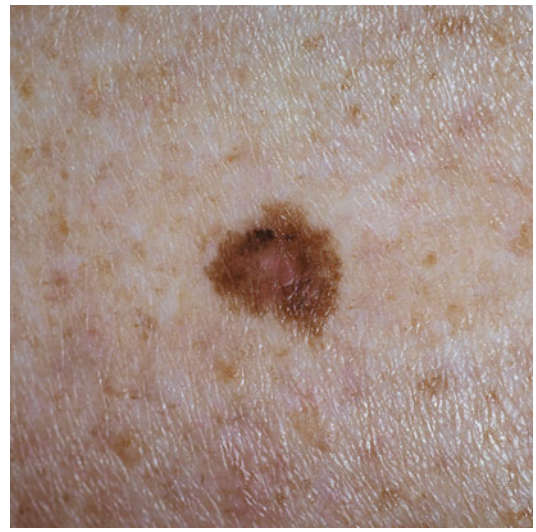


Fig. 3 Melanoma. (Image provided by Dept of Dermatology, UNMC)

Epidemiology

Melanomas account for the most skin cancer deaths, yet make up only 1% of all skin cancer types [11]. While older men are most often affected, melanomas are one of the most common cancers found in the younger population. Superficial spreading and lentigo maligna melanomas occur slightly more often in females. In the United States, about 100,000 cases of melanoma are diagnosed a year and approximately 7000 deaths are attributed to melanoma. Earlier diagnosis has led to a rise in the 5-year survival rate. Affected areas include the torso, head and neck in males, and the extremities in females.

Classification

The four major subtypes are: superficial spreading, nodular, lentigo maligna, and acral melanoma.

Superficial Spreading Melanoma

This subtype represents 70% of melanomas. It commonly arises from an existing nevus, has multiple color variations, and spreads gradually in a horizontal fashion. It is found on backs and lower extremities.

Nodular Melanoma

Representing 15–30% of cases, this second most common subtype of melanoma appears as a

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uniformly dark, raised lesion, with possible associated ulceration or hemorrhage. Nodular melanomas can have a depth of greater than 2 mm at the time of diagnosis.

Lentigo Maligna Melanoma

Occurring in 10–15% of cases, this less common subtype of melanoma arises from a lentigo and spreads horizontally; it is seen in older patients in sun-exposed areas on the face and forearms.

Acral Melanoma

This subtype makes up less than 5% of melanomas, but is common in darker-skinned individuals. It presents as a dark macule or patch with raised areas and if often seen on soles or palms. It can also show signs of bleeding or ulceration.

Less common melanoma subtypes include **amelanotic melanoma** and **subungual melanoma**. In amelanotic melanoma, the lesion is pink in color and expands over time. In subungual melanoma one can see a darkly pigmented band within the nail, arising out of the nail matrix. It can also present as a mass below the nail plate.

Approach to Patient

Diagnosis

History

Patients usually present with a new or changing skin lesion. Melanomas can be symptomatic (pruritic or tender) and associated with bleeding and scabbing. When reviewing the patients' history, several risk should be explored. These include a family history of melanoma, atypical or larger nevi, sun exposure vocationally or recreationally, sunburns at a young age, fair complexion, tanning-bed exposure, immunosuppression, or advanced age.

Physical Examination

Most melanomas present with discoloration and uneven pigmentation. Variations in color include brown, black, pink, pale, or gray tones. The margins of these lesions are irregular and the surfaces uneven. The clinical diagnosis can be challenging [12]. When dermoscopy is utilized, it improves the sensitivity and specificity and assists in differentiating between an atypical nevus and a melanoma. Beyond the lesion itself, examining the surrounding lymph nodes is advised.

Laboratory and Imaging

A definitive diagnosis is made through histopathology. When metastases are suspected, imaging of the chest and CT imaging may be useful in staging. Testing of liver enzymes should also be considered.

Special Testing

Lesions suspicious for melanoma should be biopsied. A complete full-thickness excisional biopsy with additional 1–3 mm margin is preferred. A punch biopsy can be useful for diagnostic purposes; it is also useful when a lesion is located on a sensitive area such as the face or a distal extremity. When a partial incisional biopsy is undertaken, it should be aimed at the most atypical section of the lesion. A very thin lesion that is less suspicious can be removed via a deep shave biopsy. A nail biopsy should entail the nail matrix. The final pathology report is key to the further work-up and ultimate treatment plan. Staging is based on the depth of the lesion (Breslow tumor thickness reflects the depth of malignant cell invasion of the dermis), the presence or absence of ulceration, and the mitotic rate. The Clark level of anatomic invasion is also taken into account. In melanomas that exceed a depth of 1 mm, a sentinel node biopsy is done to determine the further prognosis.

Differential Diagnosis

Pyogenic granuloma, pigmented BCC, common or atypical melanocytic nevus, traumatized nevus, blue nevus, solar lentigo, hemangioma, inflamed SK, and dermatofibroma.

Treatment

Tumor thickness is used in guiding further skin excision and is the most important prognostic factor. Survival diminishes with increased thickness. At 1 mm or less, the 10-year survival is 92%; at >4 mm, the rate drops to 50% [13].

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The re-excision margin varies depending on the Breslow depth. A margin of 0.5 cm is needed for melanoma in situ, 1 cm in melanomas of <1.0 mm depth, 1–2 cm in those with depth of 1.01–2.0 mm, and 2 cm in melanomas deeper than 2.0 mm.

Medications

Off label use of topical imiquimod (Aldara) has been explored. Vaccines may also play a role in adjuvant therapy.

Referrals

Whenever changes in an existing mole are observed, or a new growing lesion is detected, referral to a dermatologist should be considered. A plastic surgery referral may also be indicated, especially when lesions are areas that are difficult to biopsy.

Counseling

Biopsies can lead to scarring. Healing can be slow and compromised on the extremities. Incomplete lesion removal may lead to further surgery.

Patient Education

Early detection saves lives. Vigilance as to new or changing skin lesions should be encouraged. Smart phone applications for melanoma detection have been developed [14].

Prevention

Limiting sun exposure and following strict sun protective measures is advised. Regular follow-up and detailed skin exams are encouraged.

Basal Cell Carcinoma (BCC)

See (Fig. 4).



Fig. 4 Basal cell carcinoma. (Image provided by Dept of Dermatology, UNMC)

General Principles

Definition

This is the most common form of skin cancer, arising out of the basal layer of the epidermis and its appendages. While it is readily treatable by a variety of methods, it can be locally invasive and destructive, or very seldom, metastasize.

Epidemiology

BCCs make up 8 out of 10 nonmelanoma skin cancers, affecting mainly Caucasian patients over age 40 with a history of extended sun exposure. The incidence increases with age. Men are more often affected than women. States closer to the equator such as Hawaii and California have a higher incidence of BCC. Overall risk factors include UV radiation, tanning beds, phototherapy, and ionized radiation. Certain phenotypes with light hair and eye color and those with a personal history of BCC are also at greater risk.

Classification Based on Histopathology

Nodular BCC

As the most common BCC lesions, these can be pigmented or nonpigmented, and often have an irregular surface or ulceration at the center.

Superficial BCC

These BCC lesions are flat, scaly, and plaque-like in presentation. A reticular infiltration can be seen.

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Sclerotic/Morphea-Form BCC

These lesions are accompanied by fibrous stroma, are whitish and have ill-defined margins.

Approach to Patient

Diagnosis

History

Patients will describe a nodule, scabbing, or ulcerating lesion, which appears to be expanding slowly over time.

Physical Examination

The majority of BCCs are located on the face (70%), with 15% found on the trunk. BCCs most often present as a singular firm nodule or papule (nodular BCC), 3–10 mm in size, which can appear pearly in nature. When ulcerated, the border can be described as rolled. BCCs can also appear flat and scaly (superficial BCC) or whitish/fibrous (morphea-form BCCs). Multiple lesions can occur. Dermoscopy is helpful in establishing the diagnosis and can show branching vessels.

Special Testing

Shave or excisional biopsy can establish the diagnosis, but a wider excision with 1–3 mm margins may be needed to sufficiently remove the BCC. Shave biopsy is preferred in areas of skin preservation.

Differential Diagnosis

Dermal nevi, epidermal inclusion cysts, sebaceous hyperplasia, and SCC can mimic nodular BCC, whereas nummular eczema, benign lichenoid keratoses, and amelanotic melanoma can look like superficial BCC. Scleroderma must be distinguished from morphea-form BCC.

Treatment

The treatment depends on the site and extent of the lesion. Cryotherapy is best used for thin, superficial BCC lesions. Mohs surgery is indicated for cosmetically sensitive regions of the face. This form of surgery involves microscopic, incremental removal of layers of the tumor, until the area is tumor free. When complete surgical excision of a BCC lesion can be undertaken, no further treatment is needed. Electrodessication and curettage can be utilized for incompletely removed lesions. Surveillance for local recurrence is advised. When BCC lesions are very large or located in difficult to treat areas, or when palliative treatment is appropriate, radiation therapy can be helpful. Light therapy is another treatment option and involves application of photosensitizing agents to the BCC.

Medications

5FU elicits an inflammatory response that causes destruction of superficial BCC lesions. Imiquimod (Aldara) 5% cream, which is typically applied daily for 6 weeks, has a similar yet more severe effect.

Counseling

Scarring can follow removal of lesions. Local recurrences can occur.

Patient Education/Prevention

Sun avoidance or sun protection through wearing of hats, sun screen, and UV-obstructing clothing is recommended, best done before age 18.

Squamous Cell Carcinoma (SCC)

See (Fig. 5).

General Principles

Definition

SCC is a malignant tumor arising from epithelial keratinocytes as a result of sun exposure or other carcinogens such as ionized radiation. It rarely metastasizes (in 2–6% of cases), and can be effectively treated when diagnosed at an early stage.

Epidemiology

SCC is generally seen in the Caucasian population, occurring more often in men over 55 years of

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Fig. 5 Squamous cell carcinoma. (Image provided by Dept of Dermatology, UNMC)

age on sun exposed areas. These men often work outdoors, but industrial workers exposed to chemicals can also be affected. Darker skinned individuals can develop SCC from other etiologies. Transplant patients on immunosuppressants are at risk for SCC. Actinic keratosis is a precursor to SCC. SCC can occur in skin damaged by sun, radiation, scars, or burns.

Classification

Bowen's Disease: This is classified as SCC in situ, and presents as a scaly, hyperkeratotic macule or plaque.

Keratoacanthoma: This is a variant of SCC, arising rapidly and presenting with a central keratotic core.

Oral SCC: This is usually a more aggressive form of SCC.

Erythroplasia of Querat (Penile SCC): Also known as Bowen's disease of the penis, this presents with an erythematous plaque on the glans and foreskin and has been linked to HPV.

Vulvar SCC: This form of SCC is also linked to HPV and can be seen in immunocompromised women.

Approach to Patient

Diagnosis

History

Most patients will notice a nodule or non-healing, often scaly scab, which arises over several weeks to months.

Physical Examination

Depending on the form of SCC, patients can present with a thick keratotic scale, an indurated papule or plaques, or an ulcerated nodule. SCC in situ often appears red and scaly. Surrounding areas should also be evaluated for lymph node involvement and other signs of sun damage. Dermoscopy can be helpful [6].

Laboratory and Imaging

If the diagnosis is in question, a biopsy can be performed. CT imaging is useful for staging purposes.

Special Testing

Shave, punch, or excisional biopsies are used for diagnostic purposes and should extend into the dermis. Excising the lesion with a 4 mm margin most often allows for removal of the tumor. Mohs surgery is needed in cases with microscopic invasion.

Differential Diagnosis

The differential diagnosis for SCC includes actinic keratosis, BCC, psoriasis, and Lichen planus. SCC in situ can present similar to nummular eczema.

Treatment

The choice of treatment is often determined in conjunction with a specialist referral to dermatology and/or plastic surgery. Many factors influence the decision including the site, size, shape, and nature of the lesion.

Localized SCC can be considered completely removed if the excisional biopsy denotes negative margins; otherwise a repeat excision must be performed.

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High-risk SCCs, and those arising on the face, are best suited for Mohs surgery. Assessment for invasion of the surrounding tissue is important.

Low-risk, small SCC (less than 1 cm in diameter) can be treated with electrodessication and curettage.

Radiation may also be indicated for certain cases, especially when the lesion is not readily accessible surgically. It can decrease the tumor size, but may lead to scarring and also telangiectasia.

Medications
Superficial SCC can be treated with 5 FU.

Referrals
Consultation with dermatology and/or plastic surgery is advised in patients with larger or high-risk lesions, and when Mohs surgery is indicated.

Counseling
Patients should be counseled about the possibility of metastases, even though it is rare. Scarring may result from treatment.

Patient Education
Sun avoidance and sun protection is advised. Since SCC may recur, clinical follow-up is considered important.

Keratoacanthoma (KA)

General Principles

Definition
This nonaggressive form of skin cancer presents as a dome-shaped nodule arising from the epithelium, and is made up of a central keratin-filled crater. It is thought to be a variant of SCC and can develop and expand rapidly.

Epidemiology
KAs occur predominantly in men over age 50 who are of Caucasian descent and have a history of sun exposure. Other risk factors include skin color, trauma, genetics, and chemical carcinogens. Most often a solitary lesion is seen on the neck, face, ears, and hands.

Approach to the Patient

Diagnosis

History
Patients present with a dome-shaped nodule marked by rapid growth over several weeks.

Physical Examination
These lesions are usually singular, 5 mm to 2.5 cm in size, skin-colored or red, nodular in shape, and firm to touch. The dome shape and central keratotic plug distinguishes these lesions. Dermoscopy cannot reliably distinguish between KAs and SCCs.

Special Testing
The diagnosis is made through both clinical and histopathological assessment. An excisional biopsy extending into the subcutaneous fat is advised. It is important to differentiate this lesion from an SCC.

Differential Diagnosis
SCC, nodular BCC, sebaceous cyst, molluscum contagiosum, Kaposi sarcoma, and dermatofiroma.

Treatment
While lesions can undergo spontaneous regression over time, this can lead to a disfiguring scar. An excisional biopsy is usually advised, especially when an SCC is suspected. When a shave biopsy is undertaken, it may need to be followed by electrodesiccation and curettage.

Referrals
A dermatology referral may be necessary if the lesion is large or in an area of cosmetic concern.

Counseling
Patients should be counseled about possible scarring. In the case of incomplete removal, a follow-up procedure may be required.

Patient Education/Prevention
Avoidance of sun exposure and wearing of sun protective clothing is advised.

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Kaposi Sarcoma

General Principles

Definition

Kaposi sarcoma (KS) is an angio-proliferative disorder associated with Human Herpes Virus 8 (HHV-8), marked by violaceous nodules. Lesions occur on the skin, but can also be found in other sites such as the oral cavity, GI tract, lymph nodes, and respiratory tract.

Epidemiology

In the United States these lesions occur predominantly in male patients and HIV patients, but also in immunocompromised individuals. Other variants of KS are noted in patients of European or African descent [2].

Classification of KS

Endemic or Classical KS: This type of KS is found in elderly males of European, especially Mediterranean descent.

African KS: This type of KS involves lymph nodes; it is seen in young men and children living in equatorial Africa.

Iatrogenic KS: This type of KS is associated with immunosuppressant therapy and organ transplants.

Epidemic KS: This type is associated with AIDS.

Approach to Patient

Diagnosis

History

Most often patients initially notice a painless ecchymotic macule or nodule. Occasionally ulceration and bleeding can occur, and larger lesions on the extremities can be of functional hindrance, especially if swelling and fibrosis accompany the lesions.

Physical Examination

Lesions typically are oval in shape, have a red or purplish hue, feel firm to touch, and can present as macules, papules, plaques, or nodules. Usually the lesions are situated in the dermis, but can erode the overlying epidermis, forming an ulcer. Lesions can become confluent and associated lymphedema can occur in extremities. In the mouth lesions commonly occur on the hard palate, but can be seen on the uvula and gingiva.

Laboratory and Imaging

On biopsy one finds an intradermal nodule with atypical endothelial cells lining the vascular channels. Pulmonary nodules and pleural effusions can be seen on chest xray (CXR). HIV testing is advised.

Special Testing

The diagnosis is made by skin biopsy.

Differential Diagnosis

Malignant melanoma, pyogenic granuloma, dermatofibroma, hemangioma, ecchymosis, and bacillary angiomatosis.

Treatment

Individual lesions can be removed by excision. Other local interventions include radiotherapy, cryosurgery, or laser surgery.

Medications

More aggressive treatment options may be necessary for complex cases and include intralesional or systemic chemotherapeutic agents. HIV treatment should be addressed in cases associated with HIV disease. In patients on immunosuppressants such as prednisone or methotrexate, consideration should be given to holding such if possible.

Referrals

Consultations may include referrals to dermatology and to oncology.

Counseling

Scarring may occur as a result of local treatments and skin biopsies. Mortality rates increase with GI or pulmonary involvement.

Patient Education

The disease can recur and careful vigilance for such is advised.

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Vascular Lesions

Hemangioma

General Principles

Definition

Hemangiomas are known as benign blood vessel growths. When they occur in early infancy, they are known to expand rapidly within the first year of life and then disappear spontaneously by age 5 years [15].

Epidemiology

Hemangiomas occur slightly more often in females.

Classification

Capillary hemangiomas of infancy: These are also known as strawberry nevi and are soft, red to purple nodules or plaques, occurring at or just after birth.

Cavernous hemangiomas: These are somewhat darker vascular malformations associated with swelling of the deeper tissues. They are often larger and can contain arteriovenous shunts. Varicosities can be seen at the skin surface.

Cherry angiomas: Also called senile angiomas or Campbell de Morgan spots, these are common, benign, red, dome-shaped vascular lesions with capillary proliferation, which increase with age.

Approach to the Patient

Diagnosis

History

Patients will notice a red or purplish skin lesion that typically appears to be enlarging over time. Adults may express concern over the cosmetic appearance of cherry angiomas.

Physical Exam

Capillary hemangiomas are often soft red to purple nodules, which do not blanch completely. They occur on the face, trunk, legs, and mucosal membranes. Cavernous hemangiomas present as soft swellings, often multinodular and blue in color, which are easily compressed. Cherry angiomas are small, red, soft papules that occur mainly on the trunk and proximal extremities; they typically blanch with pressure.

Laboratory and Imaging

The diagnosis of hemangiomas is made clinically. Deeper or larger lesions may require imaging to evaluate the full extent of the lesion. Specialist referral is recommended when hemangiomas are found overlying the midline of the spine, as underlying neural tube defects can be associated with such.

Differential Diagnosis

Pyogenic granuloma, melanoma, and bacillary angiomatosis.

Treatment

Most hemangiomas involute spontaneously by age 5 years. Deeper lesion may not recede completely, especially when mucous membranes are involved. Pulse-dye laser treatment can be used for lesions that are larger or impair function. No treatment is needed for cherry angiomas, unless cosmesis is a concern. Pulsed-dye laser, cryotherapy, and electrocautery can be utilized.

Behavioral

Most hemangiomas are asymptomatic but can present cosmetic concerns. Those that are larger and exposed can become ulcerated and may need to be protected.

Medication

Both prednisone and propranolol have been successful in the treatment of hemangiomas.

Referrals

Pediatric surgery or pediatric dermatology consultations should be considered in larger hemangiomas, or those prone to bleeding, ulceration, or scarring.

Counseling

Guidance to parents is important, especially when awaiting spontaneous resolution of hemangiomas

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over time. Medical and surgical treatments are accompanied by possible side effects such as scarring or depigmentation. Adults with cherry angiomas can be reassured.

Patient Education
Expectant management may suffice in hemangiomas. Cherry angiomas will likely become more numerous with age.

Angiokeratoma

General Principles

Definition
Angiokeratomas are vascular lesions, likely formed by increased venous pressure within dilated superficial dermal blood vessels, with hyperkeratosis of the overlying epidermis. Most commonly these lesions occur on the genitalia as red-to-purple papules.

Epidemiology
The onset of these lesions is typically between 20 and 50 years of age.

Classification
Angiokeratoma of Fordyce: Multiple angiomas are seen on the scrotum or vulva.

Solitary Angiokeratomas: A single lesion can be present.

Fabry-Anderson Syndrome: This syndrome is marked by numerous cutaneous angiokeratomas forming around puberty and is associated with an X-linked inborn error.

Other Vascular Malformations
These include Angiokeratomas of Mibelli, occurring on the dorsal aspects of digits.

Approach to the Patient

Diagnosis

History
Patients typically report the onset of red, purple, or black papules that can bleed with trauma.

Physical Exam
These discolored papules are usually 2–3 mm in size and most often occur on the scrotum and vulva. Vascular lacunae can be seen with dermoscopy.

Special Testing
No specific testing is required. Dilated blood vessels can be seen if a biopsy is performed.

Differential Diagnosis
Melanoma, hemangioma, Kaposi sarcoma, and pyogenic granuloma.

Treatment
Lesions can be removed by excision, electrodessication, and curettage or laser therapy. This is usually only done for cosmetic purposes.

Referrals
When Fabry-Anderson Syndrome is suspected, referral for treatment of the underlying disease is indicated. A dermatology consult is helpful when considering laser therapy.

Counseling
Patients should be cautioned that scarring can result from treatment of these lesions.

Patient Education
Since these lesions often occur on the genitalia, patients may need to be reassured that these findings are not associated with sexual transmission.

Venous Lake

General Principles

Definition
These lesions arise out of dilated venous capillaries, are usually dark-blue to purple in color, and are most often seen on the lips, face, and ears of older patients.

Epidemiology
Venous lakes occur in men/women after age 50 years, mainly on areas of sun-damaged skin.

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Approach to the Patient

Diagnosis

History
Venous lakes usually appear without symptoms, but can bleed if traumatized or become tender when thrombosed.

Physical Exam
Venous lakes are dark-blue to purple, round or oval papules to nodules. They are usually compressible (unlike blue nevi) and soft and can appear grapelike in structure on detailed examination [2].

Special Testing
None needed, as the diagnosis is made clinically.

Differential Diagnosis
Nodular melanoma, pyogenic granuloma, and Kaposi sarcoma.

Treatment
Lesions do not usually regress spontaneously. If cosmetic treatment is desired, or the lesion is traumatized and bleeds often, vascular laser treatment or electrocoagulation can be pursued.

Referrals
If the lesion undergoes change or seems atypical, a dermatology referral may be indicated.

Counseling
Lesions tend to stabilize over time. If treatment is pursued, scarring could result.

Patient Education
Sun protection is advised, and further sun exposure should be avoided.

Pyogenic Granuloma

General Principles

Definition
This is a fast growing, red or dark colored vascular nodule, seen on the skin or mucosa, often arising in response to localized trauma. It is made up out of rapidly proliferating endothelial cells and fibroblasts.

Epidemiology
Pyogenic granulomas occur most often in the second and third decade of life and during pregnancy. Both men and women are equally affected.

Approach to Patient

Diagnosis

History
Patients will present with a new nodule, which has often only been present for a few days or weeks. At times there is a preceding history of trauma to the skin – and while tenderness may be reported, recurrent bleeding from the sight can be common.

Physical Examination
Pyogenic granulomata present as red to purple, small, pedunculated single papules or nodules. Their surface is usually smooth, and can be covered by a yellow discharge. They appear friable, can have erosions, and bleed rather easily. These lesions most often occur on fingers and toes, or on the torso [2].

Special Testing
Pathological evaluation can differentiate lesions from amelanotic malignant melanoma.

Differential Diagnosis
Bacillary angiomatosis, angiosarcoma, melanoma, and Kaposi sarcoma.

Treatment
Surgical removal via shave biopsy is advised, followed by electrodessication or curettage of the base of the lesion. Since there can be a fair amount of bleeding involved, silver nitrate or aluminum chloride may need to be applied topically for hemostasis. Recurrence is possible following incomplete removal of the lesion.

Referrals
In atypical presentations, or if lesion recur or are numerous, a dermatology referral is advised.

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Counseling
Surgical removal may lead to scar formation.

Patient Education
Follow-up is advised if the lesion recurs or if the healing seems incomplete.

Nonpigmented Nonvascular Lesions

Dermatofibroma

See (Fig. 6).

General Principles

Definition
Dermatofibromas are common, benign, dermal fibrous lesions made up of histiocyte cells. They occur on the lower extremities, and often arise as a result of minor trauma such as a local insect bite. Synonyms include solitary histiocytoma.

Epidemiology
These lesions occur most often in adults – more frequently in women.



Fig. 6 Dermatofibroma. (Image provided by Dept of Dermatology, UNMC)

Approach to Patient

Diagnosis

History
Dermatofibromas appear over months to years; patients might recall minor trauma to the skin, or notice mild tenderness or itching associated with the lesion. Most lesions remain stable, but can regress spontaneously.

Physical Examination
Dermatofibromas present as solitary firm nodules or papules on the legs and arms. They are <1 cm in size and are typically pink or brown in color. By applying lateral compression, one can elicit the tell-tale "dimpling sign." The center of the lesion can show post-inflammatory hypo- or hyperpigmentation.

Special Testing
Dermoscopy shows a central scar-like lesion with peripheral hyperpigmentation. If the lesion is removed for cosmetic reason, or because of uncertainty of the diagnosis, Spindle cells can be recognized on dermatopathology. Uncommon histological variants of dermatofibromas exist.

Differential Diagnosis
Lesions that mimic dermatofibromas include dermatofibrosarcoma protuberance, malignant melanoma, hypertrophic scar formation, BCC, melanotic nevi, keratoacanthoma, and pilar cysts.

Treatment
No treatment is required, but if the diagnosis is uncertain, the lesion becomes symptomatic or undergoes changes, or if the patient desires removal for cosmetic purposes, this is best done by a punch or elliptical excision. Cryotherapy can treat protruding lesions that become irritated.

Medications
No topical agents are indicated.

Referrals
If the diagnosis seems uncertain, a dermatology referral may be in order.

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Counseling
Removal of the lesion may result in a scar.

Patient Education
Most dermatofibroma can be observed; re-evaluation is advised for changing lesions.

Acrochordon or Skin Tag

General Principles

Definition
Acrochordons are outgrows of normal skin, appearing as pedunculated lesions on stalks.

Epidemiology
Acrochordons increase in number with age, obesity, and pregnancy. They are also associated with diabetes.

Approach to Patient

Diagnosis

History
Patients notice skin tags in areas of increased friction around the neckline, axilla, inguinal, or inframammary regions. They often report snagging of the skin tags on jewelry or clothing.

Physical Examination
Whereas most skin tags are flesh-colored pedunculated lesions, they can turn red or black when becoming irritated or undergoing torsion.

Special Testing
Acrochordons are diagnosed clinically.

Differential Diagnosis
Neurofibroma and nevus.

Treatment
No specific treatment is required. If removal is desired, fine-grade scissor removal, cryotherapy, or electrodesiccation are effective. Larger lesions may require local anesthesia with 1% lidocaine with epinephrine. Hemostasis can be accomplished through use of aluminum chloride or silver nitrate.

Medication
No medication is routinely advised.

Referrals
No referrals are usually needed.

Counseling
Use of silver nitrate can lead to skin pigmentation.

Patient Education
Lesions do not typically recur.

Keloids

General Principles

Definition
Hypertrophic scars and keloids arise from an excessive fibroproliferative tissue response following injury to the skin. While hypertrophic scars are limited to margins of the original wound and can regress, keloids extend beyond the injury site into the surrounding skin and do not diminish over time.

Epidemiology
Keloids often occur in the third decade, affect men and women equally, and are most prevalent in patients with darkly pigmented skin. They are often seen on the trunk, earlobes, shoulders, and upper back. While they can arise spontaneously, especially on the sternal region, they usually follow an injury to the skin such as with vaccination, acne, an abrasion, a piercing, cryosurgery, or an excision.

Approach to Patient

Diagnosis

History
Most often patients report an injury to their skin. While the lesion is usually asymptomatic, some keloids can be tender or pruritic.

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Physical Examination
Lesions can be skin-colored, but often seem red in appearance. They have a firm, hard texture and are often linear in configuration. Keloids extend beyond the borders of the original injury.

Special Testing
This is usually a clinical diagnosis and does not require specialized testing.

Differential Diagnosis
Dermatofibrosarcoma protuberans, sarcoidosis, desmoid tumor, and foreign body granuloma.

Treatment
Lesions that are excised can recur, unless adjunctive therapy is targeted at limiting reformation, and is best undertaken by a plastic surgeon or very experienced surgeon. Vascular scars may respond to laser treatment.

Medications
Intralesional triamcinolone (0.1–0.5 ml of the 10–40 mg/ml strength) may reduce the size and volume of the lesion – reduce the tenderness or pruritus – and potentially flatten it. This can be repeated monthly if needed. Combination therapy with FU has also been used. Imiquimod may also show some efficacy.

Referrals
Patients with larger or more symptomatic keloids may benefit from a referral to a plastic surgeon or dermatologist.

Counseling
Hypertrophic scars may regress, but keloids can continue to expand over time. Removal of these lesions may lead to further scarring or skin damage.

Patient Education
These lesions are considered to be benign, but can be associated with emotional distress in patients. If any changes or enlargement of these lesions occurs, re-evaluation may be necessary. Patient may want to avoid elective cosmetic surgery if they have a tendency to form keloids or hypertrophic scar tissue.

Lipoma

General Principles

Definition
A lipoma is a small soft tissue growth located in the subcutaneous tissue, consisting of mature fat cells (adipocytes) within a fibrous capsule. Lipomas are the most common benign soft tissue neoplasms.

Epidemiology
These lesions typically are seen in adults with increased adipose tissue.

Classification
Hereditary Multiple Lipomatosis: This is an autosomal dominant condition, occurring predominantly in men.

Pleomorphic Lipomas: These lipomas consist of both adipocytes and giant cells.

Angiolipomas: These lipomas are marked by capillary vessels in addition to adipocytes.

Spindle Cell Lipomas: These lipomas contain spindle cells.

Approach to Patient

Diagnosis

History
Patients will typically report a soft, non-painful lump underneath their skin.

Physical Examination
Palpation reveals a soft, round to oval, non-tender subcutaneous mass, ranging from 1 to 10 cm in size. It can be multilobulated. Patients can have several lipomas. Certain cases are linked to a genetic condition called familial multiple lipomatosis.

Special Testing
Most lipomas are diagnosed clinically. Ultrasound examination can confirm the diagnosis if needed. Rapidly expanding lipomas can be suspicious of liposarcomas – and can be further assessed through MRI studies.

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Differential Diagnosis

Epidermal cysts, liposarcomas, and ganglion cysts.

Treatment

Most lipomas do not require any treatment. Large or tender lipomas, or those that are of cosmetic concern, can be surgically excised. Various techniques can be utilized, including elliptical excision of the skin with subsequent dissection of the lipoma from the surrounding tissues, followed by skin closure. Smaller incisions may also suffice, with extrusion of the lipomatous tissue through the incisional opening. If the lipoma is of a significant size, liposuction can be utilized.

Medications

In order to shrink lipomas over time, triamcinolone 10 mg/ml can be injected monthly over several months.

Referrals

Large lipomas, or those situated in anatomically intricate regions, may be best referred to a dermatologist or surgeon.

Counseling

Potential scarring can result from treatment. Recurrences are uncommon.

Patient Education

While these lesions are usually benign, and reassurance suffices, those that expand rapidly or become painful should be reevaluated.

Epidermal Cyst

See (Fig. 7).



Fig. 7 Epidermal cyst. (Image provided by Dept of Dermatology, UNMC)

General Principles

Mucocutaneous cysts are made up of a closed sac, filled with semisolid material arising from the epithelium that lines the sac. Pseudocysts are made up of mucin from underlying joint space (digital mucinous cyst) or occur with rupture of minor salivary gland (mucocele).

Definition

Epidermal cysts are formed within the epithelium of a hair follicle; they contain keratin, not sebum.

Classification

Milia: Milia are 1–2 mm superficial, firm keratin-containing subepidermal cysts occurring on the face. They are common in newborns.

Epidermal inclusion cysts: These improperly called "sebaceous cysts" are keratin containing cysts that occur secondary to traumatic implantation of epidermis within the dermis.

Ruptured epidermal cysts: These cysts are marked by rupture of their thin wall and associated severe local inflammatory responses.

Epidemiology

Epidermal cysts occur in young to middle aged individuals and are more frequently seen in men.

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Milia occur in infants to adults, occurring equally in men and women.

Approach to Patient

Diagnosis

History
Patients describe a small bump with a central punctum, often presenting insidiously. These lesions can become painful when inflamed or infected.

Physical Exam
On exam one finds a dermal/subcutaneous nodule (0.5–5 cm in size), with an overlying skin pore, and pasty, malodorous keratin contents – occurring on either the face, neck, trunk, or scrotum. This nodule can appear inflamed, especially when rupturing spontaneously. Infected cysts are usually large and fluctuant.

Laboratory Testing
Culture is not advised.

Special Testing
Pathology is to be pursued if there is an unusual presentation.

Differential Diagnosis
Keratoacanthoma, lipoma, abscess, pilar cyst, ganglion cyst, and dermoid cyst.

Treatment
While observation is encouraged in small, asymptomatic cysts, surgical excision is advised in larger, symptomatic cysts. Incision and drainage of a fluctuant cyst is indicated, with complete removal advised only after the inflammation has resolved.

Excision can be done through 3–4 mm incision or punch biopsy, first removing the cyst contents and then pulling out the cyst itself through the incisional opening [16]– or via a larger incision.

Behavioral

Medications
No antibiotics are advised for ruptured cysts, except when surrounding cellulitis is present.

Referrals
Patients can be referred to a dermatologist or plastic surgeon if cosmetic concerns exist.

Counseling
Cyst recurrences are possible, especially when incompletely removed. Local scarring may occur.

Patient Education
Patient should be counseled about possible cyst enlargement or rupture.

Oral Lesions

General Principles

Oral lesions that cannot be rubbed off and that remain visible even after irritation has resolved, are suspicious of being premalignant, especially if they are located on the ventral surface of the tongue or the floor of the mouth.

Definition

The terms “leukoplakia” and “erythroplakia” refer to white and red mucosal, intra-oral lesions, respectively. Whereas certain lesions may represent hyperkeratosis or be caused by local irritation, at least 25% (or up to 80% in erythroplakia) may eventually progress to oral cancer.

Epidemiology

Leukoplakia typically occurs between age 40 and 70 years, and is more common in men. Risk factors include exposure to HPV, tobacco, and alcohol.

Classification

Leukoplakia: White, distinctly defined or raised mucosal area

Erythroplakia: Localized, red area often arising within plaque of leukoplakia

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Oral Hairy Leukoplakia : Variant of leukoplakia, associated with EBV, in patients with HPV

Approach to the Patient

History

Patients often do not report any symptoms, and these lesions may go undetected for an extended period of time, with only occasional discomfort or episodes of bleeding.

Physical Exam

White plaque-like or verrucous lesions (with or without ulceration) or red velvety areas are seen within the mouth, affecting the lower lip, tongue, sublingual region, or buccal mucosa. Lymph nodes may be enlarged.

Laboratory Testing and Imaging

Biopsy of these lesions is advised to exclude dysplasia or carcinoma, especially in tobacco users. Referral to specialist such as an oral surgeon may be indicated.

Differential Diagnosis

Condylomata accuminata, lichen planus, oral candidiasis, SCC, and bite callus or hyperkeratosis.

Treatment

Surgical excision of lesion advised; CO_2 laser or cryotherapy may also be used. Close follow-up is important.

Behavioral

Avoidance of tobacco use or other irritants such as alcohol is advised. HPV vaccinations may reduce incidence of oral cancers.

Referrals

Oral surgery or ENT referral indicated for removal of lesions or further consultation.

Patient Education

Patients should be counseled regarding close observation for recurrences and any new intraoral lesions, as well as avoidance of any possible triggers.

Surgical Techniques

The decision as to which surgical technique to employ hinges on various factors, including whether the nature of the lesion is malignant or benign. It is also important to consider the location of the lesion (slower healing anticipated for lower extremity lesions/wounds), the skin type of the individual (e.g., with regard to keloid formation) and the possible complications such as scar formation.

The least invasive technique may be best for good cosmetic results, but if malignancy is presumed, care should be taken to remove the entire lesion carefully – with an adequate margin, such as through an elliptical excision. A punch biopsy is also suitable for the complete removal of a smaller lesion.

Cryotherapy

This can be used for a variety of lesions, including actinic keratosis, thin BCC, verrucae, and seborrheic keratosis. Shorter freezing cycles lasting 5–15 s are sufficient for thin lesions or areas with delicate skin. Longer freezing cycles of 30 s are often required for thicker lesions such as seborrheic keratosis or BCCs. Side effects include hypopigmented scar formation and potential incomplete eradication of lesion.

Punch Biopsy

This technique is helpful for removal of small skin lesions such as atypical nevi as well as for determination of the underlying pathology of a lesion. After cleaning of the skin, local anesthetic is injected, after which a punch is used to remove the lesion via gentle pressure and rotation of the punch, until the dermis is penetrated and the subdermal fat is reached. The specimen is then sent to the pathology lab. The wound should be approximated with 1–2 sutures if a larger punch (4–6 mm or greater) is used. Smaller wounds can heal through secondary intention.

Shave Biopsy

This method can be used to remove benign lesions such as skin tags, and dermal nevi, as well as pyogenic granulomata. It is also suitable for removal of superficial BCC and for diagnostic purposes, except for lesions potentially representing melanoma, as full

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thickness depth is vital for staging. A Dermablade, razor blade, or scalpel can be used after the lesion has been marked, cleaned, and local anesthetic has been injected. Thickness up to the mid-dermis can be achieved; the specimen is then sent to pathology. If hemostasis is needed aluminum chloride (Drysol), silver nitrate or pressure can be applied. Silver nitrate may leave a stain.

Excisional Biopsy

This technique is best suited for removal of sebaceous cysts, lipomata, BCC, or SCC, and suspected melanomatous lesions. After marking and cleaning the skin area, local anesthetic is injected and the lesion removed with a margin of approximately 3 mm. An elliptical excision along the skin lines may provide the best cosmetic effect. The specimen is sent to pathology. Interrupted sutures are used to approximate the wound margins.

Curettage and Electrodessication

This technique can be used to treat an incompletely removed small or superficial SCC or BCC, a pyogenic granuloma, or as part of the destruction of the base of a keratoacanthoma. It is also useful to destroy small benign skin lesions. After cleaning of the skin and injection of the local anesthetic, the curette is used to remove abnormal tissue, until the firm base of normal skin tissue is reached. Electrocautery is applied at the base and the cycle of curettage and cauterization is repeated two more times. Hemostasis is accomplished through the cauterization itself. This technique may leave a scar.

Sun Exposure Protection

Basic Principles

It is best to avoid sun exposure between mid-morning and mid-afternoon (10 am and 2 pm). Sun burns occur quicker at higher altitudes and especially in those with fairer complexions.

UVA and UVB rays are transmitted through the atmosphere; some of the UVB rays are absorbed by the earth's ozone layer. UVA rays are thought to be more damaging, can penetrate glass, and reach the deeper skin layers such as the dermis. UVA rays can be found in tanning beds and causes wrinkling, photo-aging, and skin cancer. UVB rays are stronger mid-day and during the summer months, causing sunburns, cataracts, and skin cancer.

Sun screens can be divided into those with a physical ingredient or a chemical ingredient. Those with a physical ingredient contain zinc oxide or titanium oxide block or reflect sun rays and scatter them before they penetrate the skin. Those with a chemical ingredient such as avobenzone, PABA, or octisalate absorb the UV rays before they damage the skin.

Broad-spectrum sunscreens provide protection against both UVA and UVB rays. Higher sun protection factor (SPF) indicates better UVB protection, with SPF of 15 blocking approximately 94% of such rays, SPF of 30 blocking 97%, and SPF of 45–50 blocking 98% of rays. A minimum of SPF 30 is recommended for sun protection, as such can reduce not only sunburn, but also actinic keratosis, SCC, and melanoma.

Sun screen should be applied in adequate amounts 30 min prior to sun exposure in order to bind to the skin. Reapplication of sunscreen is important, especially after sweating or water activity, at least every 2 h. Even on cloudy days, up to 80% of UV rays reach the earth.

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Selected Disorders of the Skin

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Disorders of Hypopigmentation

Vitiligo

Vitiligo is an acquired loss of pigmentation characterized by the absence of epidermal melanocytes. The destruction of melanocytes is thought to be autoimmune in nature, but the pathogenesis is not understood. It is the most frequent cause of depigmentation; approximately 1–2% of the population is affected with no propensity for gender or race. There is a positive family history in 30% of cases, lending to a relatively strong genetic component, and half of all cases of vitiligo occur prior to the age of 20 but can occur at any age [1]. Vitiligo is further classified as type A or type B. Type A is three times more common, more generalized, and more associated with immunologic diseases. Type B is less common, more rapidly progressive, but less generalized in appearance and follows a dermatomal appearance [2]. Lesions are milk-white hypopigmented macules and patches with discrete margins, which are symmetrically distributed [3]. Commonly affected areas for both types include the face, backs of hands, axillae, and genitalia. The scalp, lips, and mucous membranes may also be affected. Vitiligo can also occur at sites of trauma, such as the elbows or knees, and in previously sun-damaged skin [2]. Vitiligo is associated with thyroid disorders in up to 30% of cases, and there are also reported associations with alopecia areata, psoriasis, adrenal insufficiency, pernicious anemia, and type I diabetes [2]. Laboratory examination to exclude these associated systemic disorders should include thyroid studies, basic chemistry labs, fasting glucose, and a complete blood count. The diagnosis of vitiligo is made by physical exam revealing well-demarcated, uniformly white macules without signs of inflammation. A Wood's lamp can be used in fair-skinned individuals to accentuate hypopigmented areas. Skin biopsy and histologic examination reveal the absence of epidermal melanocytes.

Available literature does not show a higher predilection in dark-skinned individuals, but easier recognition of skin manifestations may increase perceived disfigurement and social stigmata in these patients. Although a benign condition, it can have a major impact on feelings of stress, self-consciousness, and sexual relationships leading to low self-esteem and depression.

Management

The goal of treatment is to restore melanocytes to the skin, which requires activation and migration of melanocytes located in the hair follicles. Therefore, skin with little hair, such as

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the hands or feet, responds poorly to treatment. Modalities should be chosen on the basis of disease severity, cost and accessibility, and treatment response. Treatment usually takes 6–12 months and should be started early in the course of disease. Combination therapies, such as phototherapy plus topical or oral steroids, are more effective than either alone at producing repigmentation [4]. Moderate- to high-potency topical steroids, or topical calcineurin inhibitors (tacrolimus [Protopic] and pimecrolimus [Elidel]), for 6–9 months are preferred for localized vitiligo [2]. Whereas narrowband ultraviolet B phototherapy (NB-UVB) is added as the disease spreads. In patients with extensive generalized depigmentation who do not respond to phototherapy, depigmentation of the surrounding skin should be considered. All patients with vitiligo should minimize sun exposure and apply broad-spectrum sunscreens to help minimize the contrast between tanned skin and hypopigmented skin.

Pityriasis Alba

Pityriasis is a common hypopigmentation skin disorder in prepubescent children with a history of atopic dermatitis. The most common sites affected are the face, neck, and arms [5]. The lesions begin as a nonspecific erythema but gradually become scaly and hypopigmented with pruritus occasionally present. It is often confused with vitiligo, but vitiligo lesions do not scale. Potassium hydroxide preparation is negative in pityriasis, distinguishing it from tinea infections. The condition is benign and improves after puberty, which can help reassure patients and their families. No treatment is necessary; however, low-potency topical steroids (applied twice daily) and sunscreens are first-line treatments [3]. High-potency topical steroids can be used on erythematous inflammatory lesions, but the depigmentation is not affected by any treatment. Pimecrolimus (Elidel) cream 1% and tacrolimus (Protopic) ointment (0.03% or 0.1%), applied twice daily, are nonsteroidal alternatives for treatment.

Tuberous Sclerosis

Tuberous sclerosis (TS) is the second most common neurocutaneous syndrome, affecting 1 in 6000 newborns, and is marked by childhood seizures and mental retardation but can affect several organ systems [6]. Congenital hypopigmented macules are generally oval or ash leaf shaped located on the arms, legs, and trunk. However, adenoma sebaceum is the most common cutaneous manifestation of TS. The lesions are small (1–5 mm), smooth, firm, yellow-pink papules with telangiectasia [7]. Skin manifestations may be the earliest sign of TS and occur in 80% of patients by 1 year of age [8]. Skin biopsy shows normal melanocytes which excludes vitiligo as the diagnosis. TS is an autosomal dominant disease, and genetic counseling should be offered in persons with a family history of TS. There is no treatment for the skin manifestations, but they offer an early window for diagnosis and referral, for the management of other clinical manifestations of TS.

Disorders of Hyperpigmentation

Pityriasis Versicolor (Tinea Versicolor)

Tinea versicolor is a common superficial fungal infection caused by *Malassezia* sp. It occurs most commonly in tropical climates and commonly affects adolescents and young adults [9]. The skin lesions (macules, patches) are generally hypopigmented, but can be hyperpigmented or erythematous, often with a fine scale which can be scraped for microscopy. It is most commonly found on the upper trunk and upper extremities in adults, but facial involvement is common in children [10]. Tinea versicolor shares common clinical findings with other skin disorders and therefore confirmation of the diagnosis with potassium hydroxide (KOH) is recommended. In one-third of individuals, a Wood's lamp will reveal yellow to yellow-green fluorescence [11]. First-line therapies include topical azole antifungals such as ketoconazole or topical adapalene (Differin) gel [12]. Topical selenium sulfide 2.5% applied for 10 min daily for 7 days and 2% ketoconazole shampoo applied to

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affected areas for 5 min prior to showering for three consecutive days are effective regimens [13]. Oral ketoconazole and itraconazole, both at doses of 200 mg/day for 5 days, are also effective and appropriate for patients with a large surface area burden for topical treatment [14]. Oral terbinafine (Lamisil) and griseofulvin are not effective in treating tinea versicolor. Hypo- or hyperpigmentation can be present even after successful treatment. The presence of scale and positive KOH preparation confirms treatment failure.

Photosensitivity Dermatitis

Phototoxic reactions are nonallergic and induced by the use of systemic or topical medications or by contact with certain plants and foods in combination with sun exposure. Skin manifestations are generally confined to sun-exposed areas and result in erythema within minutes to hours of sun exposure [15]. Reactions can range from imperceptible erythema followed by prolonged hyperpigmentation to a sunburn-like reaction, edema with vesicles, and bullae [16]. Common medications associated with photosensitivity include antibiotics (fluoroquinolones, sulfonamides, and tetracyclines), diuretics (furosemide, hydrochlorothiazide), diltiazem, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and topical retinoids. Common foods include lemons, limes, celery, dill, and carrot juice [15]. Treatment is removal of the offending agent. When this occurs, the eruption generally resolves spontaneously. Oral steroids may be needed for severe cases with a significant inflammatory response. Avoidance of the offending agent (medication or food), direct sunlight, and tanning facilities is paramount. The use of clothing with ultraviolet filters and sunscreen can minimize the risk of a photosensitivity reaction.

Lichen Planus

Lichen planus (LP) is an inflammatory skin and mucous membrane reaction of unknown etiology. Mean age of onset for men and women is in the fifth decade of life, and it is rare in children younger than 5 years of age. A positive family history is found in 10% of patients. In the past, it has been thought that liver disease is a risk factor for cutaneous LP, specifically hepatitis C infection [17]. However, this association is based on studies showing weak associations and prevalence rates that range from 0% to 63%. Therefore, screening for hepatitis C in patients with diagnosed lichen planus is also controversial. Medications such as ACE-inhibitors, beta-blockers, and thiazide diuretics have been implicated in LP eruptions.

Clinical Presentation

Clinical features are characteristic and follow the six P's of lichen planus: pruritic, planar, polyangular, purple, plaques, or papules. The planar surface reveals a lacy, reticular pattern of crisscrossing whitish lines (Wickham's striae). Patterns can include annular, diffusely papular, or linear and most commonly affect ankles, volar surfaces of the wrists, forearms, and legs [18]. The clinical course is unpredictable as spontaneous remission can occur in a few months, but most commonly, LP lasts for approximately 4 years. Mucosal LP can occur with or without cutaneous eruptions; oral lichen planus is associated with concomitant vulvovaginal lesions 25% of the time [18]. Cutaneous manifestations can be erosive or nonerosive and can arise on the tongue, lips, buccal mucosa, glans penis, and anus. While a skin biopsy is the gold standard for diagnosis, the diagnosis usually can be made clinically by history and characteristics on physical exam.

Treatment

High-potency topical steroids (clobetasol, fluocinonide) are used as initial treatment for cutaneous and oral LP. Intralesional (triamcinolone acetonide 5–10 mg/ml every 3–4 weeks) and oral steroids (4 week course and taper of prednisone) can also be used for hypertrophic and generalized severely pruritic LP, respectively [17]. Azathioprine can be used as an alternative

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to steroids. Phototherapy with narrowband UVB or PUVA can also be used for generalized disease. Cyclosporine (6 mg/kg/day) is reserved for patients with severe disease. Calcineurin inhibitors, such as topical tacrolimus (Protopic) and pimecrolimus (Elidel), and aloe vera gel have all been shown to be effective in treating mucous membrane LP if topical steroids are not tolerated [17]. Antihistamines can be used as adjunctive therapy for intense pruritus.

Cutaneous Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disorder that is potentially fatal. The disease has no single diagnostic marker and is diagnosed using a combination of clinical and laboratory criteria [19]. Diagnosis and treatment can prevent significant morbidity and mortality. The prevalence of the disease is higher in African American females and persons of Hispanic and Asian descent.

Clinical Presentation

Patients with SLE will present with myriad of symptoms; however, cutaneous manifestations are the most common sign. General symptoms such as fatigue and fever (in the absence of infection) are also common. There are three subsets of cutaneous SLE: chronic (discoid), subacute, and acute lupus erythematosus [20]. Chronic type lesions are sharply demarcated erythematous raised lesions that can be round (discoid) and may have a scale. Lesions are normally found distributed asymmetrically on the face and scalp and can last for months. Rheumatologic lab tests such as antinuclear antibody (ANA), anti-double-stranded (ds) DNA, and erythrocyte sedimentation rate (ESR) are usually normal. Subacute lesions can be induced by medications such as hydrochlorothiazide and calcium channel blockers. They can be papulosquamous or annular-polycyclic and occur on the trunk, sparing the knuckles, axillae, and lateral part of the trunk. Subacute lesions are rarely noted below the waist; ANA, ds-DNA, and ESR are usually positive, and lesions are likely to recur [20]. Classically, acute lesions present as a superficial, non-pruritic, erythematous plaques on sun-exposed areas of the body. The face (butterfly rash), chest, shoulders, extensor surfaces of the arms, and dorsal aspect of the hands are the most common areas. Acute lesions are almost always associated with SLE, whereas other types are less strongly associated. Cutaneous SLE is a clinical diagnosis but confirmatory skin biopsy may be needed when diagnostic uncertainty is present. Both non-scarring and scarring alopecia occur in more than 20% of cases of SLE [20].

Treatment

Photosensitivity is present in all types of cutaneous SLE, and ultraviolet rays from the sun can both induce or exacerbate cutaneous symptoms. Patients should avoid exposure to direct sunlight and use a daily broad-spectrum sunscreen with a sun protection factor (SPF) of 15 or higher [20]. Topical corticosteroids are first line for the treatment of all forms of cutaneous SLE and are used up to three times a day if needed, even on the face. It is common to start with a low- to medium-potency steroid and advance to high potency in those who do not respond. An alternative to corticosteroids is topical calcineurin inhibitors. If either of these treatments fail, antimalarial medications such as hydroxychloroquine or chloroquine are indicated [20]. Dapsone can be used when antimalarials fail or are not tolerated. Third-line therapies include azathioprine, methotrexate, and isotretinoin. Oral corticosteroids should be reserved for patients that fail topical steroid treatment or have a large burden of disease and fail antimalarial treatment.

Corns and Calluses

Corns and calluses result from hyperkeratosis associated with stimulation of the epidermis secondary to chronic pressure or friction on the skin [21]. Risk factors include poorly fitting shoes

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and anatomical pathology (bunions, hammer toes, claw toes, elevated metatarsals, and varus or valgus inverted hind foot) leading to abnormal pressure points on the foot. Hyperkeratosis is a normal protective physiologic response; however, it becomes pathologic when the corn or callus becomes large enough to cause symptoms.

Clinical Presentation

Because structural abnormalities are an important risk factor, a thorough examination of the foot and ankle is paramount in the evaluation of corns and calluses. Corns are distinguished from calluses often by location as well as the presence of a central conical core of keratin. They are usually located over non-weight-bearing surfaces and are painful when direct pressure is applied. Two subtypes of corns exist: the hard corn and the soft corn. Hard corns are typically located on the dorsolateral aspect of the fifth phalanx or the dorsum of the interphalangeal joint of the lesser toes [21]. The absorption of an extreme amount of moisture from perspiration between the toes leads to soft corns. They most commonly occur between the fourth and fifth web space and are caused by wearing a shoe that is too tight across the toes. Calluses typically form at sites of friction, pressure, and irritation such as the heel or under metatarsal heads. In contrast to corns, calluses do not possess a conical core and have undefined margins [21]. Both entities can be painful and interfere with daily activities.

Corns and calluses are of particular concern for individuals with peripheral arterial disease or diabetes. These patients classically have significantly reduced sensation and pain perception in the distal extremities leading to an increased risk of tissue breakdown, ulceration, and infection.

Management

Removal or redistribution of pressure is the first-line treatment for corns and calluses. Orthotic devices, inserts, or changing footwear can be helpful in patients with foot abnormalities, but the devices vary greatly and preclude recommendations. Donut pads and metatarsal bars can help redistribute pressure. Symptomatic relief of a hard corn can often be achieved through debridement of the lesions and removal of the keratin plug [21]. Patients with a soft corn should be advised to wear shoes with a roomy toe box, low heels, and soft upper portion. Keratinolytic medications (40% salicylic acid plaster) should be used to remove the excessive keratin. Paring down the lesion with a sharp blade is also an option. Appropriate patients (nondiabetics) can be instructed to use a pumice stone or emery board, after soaking the foot in warm water, to help reduce the size of the lesion.

If conservative treatments do not achieve symptomatic relief, corrective surgery may be necessary. A number of procedures exist to correct the underlying cause rather than simply excise the hyperkeratotic area.

Nail Abnormalities

Physical examination of the nails is often overlooked by family physicians, but may reveal localized abnormalities that should be treated or offer a window to an underlying systemic disease requiring further workup. The three most common conditions of the nails the family physician encounters are onychomycosis, ingrown toenails, and subungual hematomas.

Tinea Unguium (Onychomycosis)

Although occurring in 10% of the general population, onychomycosis is much more common in the older adult occurring in 20% of those older than 60 years and 50% of those older than 70 years [22]. Toenails are affected more often than fingernails and are most often caused by dermatophytes of the *Trichophyton* genus. There are five classes of onychomycosis based on morphologic appearance [23]. Distal onychomycosis is the most common and, as its name implies, affects the distal aspect of the nail. Proximal subungual infections invade the nail plate from below

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and cause the nail to separate. This pattern is the most common form in patients with human immunodeficiency virus infection (HIV). Superficial infection pattern appears to have powder-like patches of transverse striae on the surface of the nail. The nail plate is not thickened as is seen in other infection patterns. Psoriatic nail changes and trauma-related dystrophy can mimic onychomycosis [24]. Histologic examination of distal nail clippings with periodic acid-Schiff (PAS) staining is the best way to diagnose onychomycosis and differentiate it from dystrophic changes resulting from psoriasis. In contrast, potassium hydroxide (KOH) testing, or nail culture procedures, yields many more false negative results (poor sensitivity). If KOH or culture methods are used, it is important to collect distal nail particles as well as subungual debris with a curette. Confirmatory testing, prior to treatment, is controversial. Immediate treatment, with terbinafine, is more cost effective than performing KOH or PAS testing first, with little impact on patient safety [25]. Fingernail infections are generally caused by the *Candida albicans* species and are associated with chronic mucocutaneous candidiasis.

Management

Onychomycosis can negatively affect patient's lives via social stigma and disruption of daily activities or prevention of leisure activities. Treatment is often difficult with a 5-year recurrence rate of approximately 30–50% [26]. Some common poor prognostic factors include >50% areas of nail involvement, significant lateral nail disease, subungual hyperkeratosis, white/yellow/brown streaks in the nail, and patients with poor peripheral circulation or immunosuppression. Oral antifungals are the treatment of choice. Terbinafine (Lamisil) is the first-line treatment with a higher cure rate, lower relapse rate, and fewer side effects than itraconazole. Continuous dosing (terbinafine 250 mg/day for 12 weeks) has been shown to be superior to intermittent treatment, but pulse dosing of itraconazole (200 mg twice a day for 1 week per month × 3 months) is an alternative to continuous dosing [23]. Routine interval laboratory testing of liver function, in persons without a history of hepatic disease, is unnecessary [27]. Complete resolution takes time (12–18 months to replace a diseased nail), and the nail surface is likely to still look infected after the 12-week treatment course. The use of oral antifungals is discouraged in patients with liver, renal, or heart disease. Superficial dermatophyte infections respond to topical antifungals and can be offered as an option. Cicloopirox nail lacquer has a low cure rate but can be offered to those who desire a trial of topical antifungal prior to initiating systemic therapy [24]. Although topical antifungals are not used to treat active onychomycosis, they can be used to help prevent recurrence. A twice-weekly application of terbinafine cream in the nail area, and between the toes, has been suggested for prevention [26]. Painful or extremely infected nails can be surgically removed.

Ingrown Toenails

Ingrown toenails are common and most commonly affect the large toe. Ingrown toenails occur when the periungual skin is penetrated by the nail, entering the dermis and causing a foreign body reaction which results in a painful toe [28]. Risk factors include tightly fitted shoes, trauma, hyperhidrosis, poor foot hygiene, or excessive trimming of the lateral nail plate. Characteristic signs and symptoms include pain, edema, exudate, and excessive granulation tissue. Indications for treatment include significant pain or infection or recurrent paronychia. Conservative therapy can be used when there is minimal inflammation and pain without purulent drainage. Frequent warm water soaking for 10–20 min, followed by application of a topical antibiotic or topical steroid several times daily, can be tried initially [29]. Other conservative methods include placing wisps of cotton, dental floss, or a gutter splint under the lateral nail edge. There is no evidence to suggest that any of these methods increases the risk of infection. Pre-procedure antibiotics are not indicated and do not reduce healing time or morbidity [30]. The most common

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surgical procedure to treat an ingrown toenail is partial avulsion of the lateral edge of the nail followed by matricectomy using 80–88% phenol. Phenolization after partial avulsion is more effective at preventing recurrence than partial avulsion alone, although there is an increase in postoperative infections [29]. The regular use of post-procedure antibiotics is not indicated.

Subungual Hematoma

Trauma to the nail and bleeding of the underlying nail bed cause immediate pain secondary to increasing pressure and separation of the nail plate. Puncturing the nail with an electrocautery device, or a red-hot paperclip, is the quickest and most effective method of draining the blood [31]. It is important to avoid the lunula (white crescent part of the nail), and its underlying nail matrix, during the procedure. No anesthesia is required for this procedure. It is important to tell patients that nail discoloration may persist until the nail has completely grown out.

Alopecia

Alopecia is defined as the absence of hair where it is supposed to be present. Growing hairs are termed anagen hairs and make up approximately 85% of all hair. They are securely anchored to the scalp and generally remain in this phase for 3 years. The resting or telogen phase lasts about 100 days and makes up the other 15% of all hair (with some in a catagen or transition phase). Normal shedding of hair occurs daily; however, abnormal hair loss can be pathologic or physiologic. Use of a wig may be recommended for management of both pathologic and physiologic hair loss regardless of cause.

Pathologic Hair Loss

There are four main types of pathologic hair loss. They are categorized according to the degree of scalp involvement (focal or diffuse), as well as the presence of or absence of scarring. Physical exam and a thorough history will yield the correct categorization of hair loss for the majority of patients. Early recognition and diagnosis are important to aid in timely treatment, which may help to prevent further hair loss.

Telogen Effluvium

Telogen effluvium is the most common form of pathologic hair loss and typically follows a major life stressor such as a serious illness or injury, childbirth, or excessive dieting/rapid weight loss. Physiological causes include anemia, thyroid disorders, and several medication classes (beta-blockers, anticoagulants, oral contraceptives). Laboratory studies may be indicated if an underlying systemic disorder is suspected [32]. Whatever the etiology, the hair follicle enters into the resting phase (telogen phase) and causes diffuse, non-scarring hair loss, without causing complete baldness. The hair follicle, in essence, resets its biological clock and undergoes a normal involutional process [33]. This process takes approximately 100 days, so hair loss is typically seen 2–3 months after the inciting event. Conversely, when the precipitating event is removed, hair loss corrects itself in about 100 days, but may last longer than 4–6 months, fluctuating with times of normal and abnormal hair loss, depending on the inciting event [33, 34]. Physical examination typically reveals generalized hair loss as well as a positive hair pull test (place 40–60 hairs between the thumb and forefinger and pull slowly to the end of the hairs) [32]. The test is considered positive if greater than 10% of the hairs are removed. Treatment consists of stress reduction or identifying and treating the medical cause [32, 33]. Although difficult at times, patients should be reassured that no medication is needed for treatment. As stress wanes, the hair follicles regain normal physiologic activity, hair loss subsides, and regrowth occurs naturally.

Anagen Effluvium

Anagen effluvium is a sudden loss of hair follicles in their growing phase and can cause 80–90% hair loss. Chemotherapy, radiation, or toxic chemicals

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typically cause this, though inflammatory diseases such as alopecia areata and pemphigus are also culprits [35]. Anagen effluvium can manifest as either patchy or diffuse hair loss. Hair shedding typically begins 1–3 weeks after starting chemotherapy and is usually complete after 1–2 months. Hairs of the scalp are the most largely effected, though there can be hair loss of the eyebrows, eyelashes, pubic hair, and axillary hair as well [36]. Hair follicle stem cells are spared from destruction; therefore, the hair loss from anagen effluvium is not permanent [37]. Scalp cooling has been shown to reduce the risk of chemotherapy-induced hair loss by 55% [38]. No medication has been shown to prevent anagen effluvium.

Alopecia Areata

Alopecia areata is characterized by rapid hair loss in a sharply defined area. Its incidence is about 0.1–0.2% of the population of the United States. The etiology is unknown, but genetic factors may play a role. The association of alopecia areata with thyroid disorders and vitiligo suggests an autoimmune etiology; however, the significance of this association is unknown. Alopecia areata manifests as a non-scarring form of focal hair loss that can occur in a single patch or multiple patches. The affected skin shows smooth, circular, discrete areas of complete hair loss. The periphery of the circular areas may have short stubs of hair that remain (exclamation point hair). The hair loss can occur at any age, but it is more common in children and young adults, with up to 66% of people affected being less than 30 years of age [32]. The onset of the hair loss is typically rapid (a few weeks) and can potentially affect the entire body (alopecia universalis) but the scalp remains the most commonly affected. Overall, as many as 50% of patients with alopecia areata will recover within 1 year; for those with 1–2 patches of focal hair loss, recovery is as high as 80% [39]. Factors associated with a high likelihood prolonged hair loss or relapse are onset in childhood, severe disease affecting scalp and the body, duration of more than a year, associated nail disease (pitting of the nail plate), or a family history of alopecia areata [40]. Unfortunately, there are currently no curative treatments for alopecia areata. Treatments help to control but do not cure or prevent the spread of alopecia areata. Intralesional injection of corticosteroids is the first-line treatment in patients with less than 50% of the scalp affected. Injection of triamcinolone acetonide (5–10 mg per ml) into the hairless patch every 2–6 weeks stimulated hair growth in 60–67% of cases. The use of high-potency topical corticosteroids has been controversial in the past; however, clobetasol propionate, 0.05%, applied to the area in a thin layer for 6 weeks and then off 6 weeks has been found to be both highly effective and safe in children [41]. Topical minoxidil (Rogaine) 5% concentration can also be used in individuals with greater than 50% of the scalp affected. It is best used in combination with other treatments, such as topical corticosteroids or anthralin. Other treatments include topical immunotherapy such as dinitrochlorobenzene, and tars, which induce an irritant or allergic contact dermatitis that promotes hair growth during healing [33].

Cicatricial (Scarring) Alopecia

Cicatricial alopecia causes permanent hair loss due to the destruction of hair follicles by inflammatory, autoimmune, or non-follicular process. It can be widespread or localized and can be classified as primary or secondary. In primary scarring alopecia, the follicle is the target of inflammation and common causes include discoid lupus, folliculitis decalvans, lichen planopilaris, acne keloid, and dissecting cellulitis of the scalp. In secondary scarring alopecia, the follicles are destroyed by a non-follicular process such as neoplasm, radiation, infection, surgery, and physical or chemical burns [40]. A biopsy is recommended to help support the diagnosis and determine the etiology. Scarring alopecia is an indication for dermatologic referral. Treatment depends upon the level of activity of the disease causing the scarring. Certain causes such as discoid lupus and lichen planopilaris may respond to topical, intralesional, or systemic steroids. Folliculitis decalvans will often respond to long-term

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antibiotic treatment with doxycycline, minocycline, erythromycin, Bactrim, or rifampin. If scarring is severe, surgical treatments including scalp stretching (removal of bald area and stretching the adjacent scalp over the removed area) or hair transplantation will be needed for treatment.

Traumatic Alopecia

Traumatic alopecia results from hair being forcefully extracted from the head or the breaking of hair shafts by friction, traction, pressure, or other physical trauma. Typical causes include cosmetic practices, trichotillomania, and pressure on the head as occurs on the occiput of infants who lie on their back. Common cosmetic practices that can cause traumatic alopecia (trichorrhexis nodes) include tight braiding, use of hair extensions, frequent brushing with nylon bristles, as well as most hair-straightening practices. Traction alopecia from braids or hair weaves can be detected along the frontal and temporal hairlines. Longstanding traction can lead to cicatricial alopecia and permanent hair loss. If no clear etiology, laboratory evaluation to include a complete blood count, iron studies, copper level, liver function tests, thyroid stimulating hormone level, and serum and urine amino acid levels is reasonable [32]. Treatment includes behavior modification to curtail hair trauma practices and/or managing underlying systemic illness that leads to increased hair fragility.

Trichotillomania is consciously or habitually plucking, cutting, or pulling hair in a bizarre manner and is a self-induced form of traumatic alopecia. Although it can be normal in children, it is closely related to obsessive-compulsive disorder in some children and adults. The mainstay of treatment is helping the patient find a different way to express their emotional needs. Psychiatric referral may be necessary.

Fungal Infection (Tinea Capitis)

Fungal infections can lead to scarring and non-scarring alopecia. Black dot tinea capitis is the most common form in the United States and preferentially affects African American children between 3 and 9 years of age [24]. Similar manifestations in adults should lead one to consider other diagnoses or consider a concomitant immunocompromised condition. Hair, within the scaly patches of hair loss, break off flush with the scalp and appear as a black dot. Diagnosis of tinea capitis can be confirmed with a Wood's lamp, fungal culture, or 10% KOH examination, but most physicians treat tinea capitis if the presentation is typical. First-line treatment of tinea capitis in children has traditionally been with 6–12 weeks of griseofulvin. Newer studies have shown that terbinafine (Lamisil) and fluconazole (Diflucan) have equal effectiveness and safety and shorter treatment courses. Terbinafine has similar efficacy in tinea capitis caused by Microsporum species but requires similar duration of treatment (6–12 weeks) as griseofulvin. Fluconazole has similar effectiveness with only 3–6 weeks of treatment [42]. Topical antifungals are not effective as they do not penetrate the hair shaft. However, concomitant treatment with 1% or 2.5% selenium sulfide shampoo or 2% ketoconazole shampoo should be used in the first 2 weeks of treatment to help decrease the risk of transmission [24]. There should be consideration of treating all close contacts with one of the aforementioned shampoo regimens for 2–4 weeks.

Physiologic Hair Loss

Androgenic alopecia (male pattern baldness) affects greater than 50% of men by 50 years of age and 40–50% of women by 60 years of age. It manifests as bitemporal hair thinning followed by loss of hair over the crown. Symptoms for women are not as severe as in men. Rapid hair loss or hair loss accompanied by pruritus, burning, or tenderness should lead one to consider other diagnoses. An association between male pattern baldness with cardiovascular disease and prostate cancer has been reported; however, the strength of the associations, if any, needs to be clarified. Treatment of androgenic alopecia includes both surgical and nonsurgical options. Medical options include topical minoxidil

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(Rogaine) and oral finasteride (Propecia). Topical minoxidil prolongs the anagen phase of hair follicles and pushes resting hair follicles into the growing phase. Minoxidil, at 5% concentration, has been found effective for both hair preservation and regrowth in both men and women but is much more effective in the preservation of existing hair. It should be applied twice daily and benefits may take up to a year to be noticed [43]. Discontinuation of the medication results in continued hair loss and use should be indefinite. There are minimal side effects associated with topical minoxidil. Finasteride is an oral type II 5a-reductase inhibitor that blocks the conversion of testosterone to DHT. At treatment dosing (1 mg per day), it has been found to decrease circulating DHT by two-thirds. When used for 2 years, the medication was able to prevent further hair loss in 83% of men between the ages of 18 and 41 [43]. As with minoxidil, treatment should continue for 12 months to assess the drug's efficacy and must be continued indefinitely to maintain that efficacy. Finasteride can cause decreased libido, erectile dysfunction, and ejaculatory dysfunction and is a pregnancy category X medication. Finasteride can also significantly decrease serum levels of prostate-specific antigen. There is weak evidence showing that combination of finasteride and minoxidil works better than either alone, and this may be an option. Platelet-rich plasma (PRP) scalp injections are a novel treatment option, but more data is needed in order to recommend this modality. Possible surgical approaches for androgenic alopecia include follicle transplant, scalp reduction, and a transition flap.

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Part XXIV

The Endocrine and Metabolic System

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Dyslipidemias

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General Principles

Definition of Dyslipidemias

Dyslipidemias refer to abnormal function and/or levels of plasma lipoproteins. In routine clinical practice, they are detected by altered plasma lipid levels, which can be elevated (hyperlipidemia) or decreased (hypolipidemia). Normal lipid levels

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are not synonymous to desirable (optimal or physiological). Hyperlipidemias are of extreme clinical importance due to being the root cause of atherosclerosis leading to atherosclerotic cardiovascular disease (ASCVD). The normal level of low-density lipoprotein cholesterol (LDL-C) is <100 mg/dL, while the non-HDL-C desirable level is <130 mg/dL. High-density lipoprotein cholesterol (HDL-C) is considered low when <40 mg/dL in men and <50 mg/dL in women. Triglycerides (TGs) are elevated when >175 mg/dL [1].

Lipids and Lipoproteins

Lipoproteins are particles composed of lipids (C, cholesterol; TGs, triglycerides; phospholipids) and proteins (apolipoproteins, Apo). The standard lipid panel (LP) measures total TG and cholesterol content in a particle (-C), but not particle count (-P), which can be measured directly by NMR technique or by surrogate markers (e.g., ApoB or ApoA1 levels). Chylomicrons are synthesized in the intestinal epithelium (TG:C ratio 10:1) and hydrolyzed at endothelial surface of capillaries by lipoprotein lipase (LPL) to chylomicron remnants (ChR), removed by the liver. The liver synthesizes very low-density lipoprotein VLDL-P (TG:C ratio 5:1), hydrolyzed by the same LPL to intermediate-density lipoprotein (IDL-P) and then low-density lipoprotein (LDL-P), which is poor in TG and rich in C. LDL-P and other ApoB-containing lipoproteins (e.g., ChR, VLDL-P, and IDL-P) may penetrate the arterial intima, promoting the development of atherosclerotic plaques. High-density lipoprotein (HDL-P, measured by surrogate markers HDL-C or ApoA1) participates in reverse cholesterol transport from plaques to the liver. However, HDL-C levels >100 mg/dL are pro-atherogenic. LDL-P are bound to LDL receptors (LDLr) on hepatocytes. This complex is endocytosed: LDL-P is degraded, while LDLr is recycled to bind more LDL-Ps. However, PCSK9 (proprotein convertase subtilisin/kexin type 9), a protein secreted by hepatocytes, binds to LDL-P/LDLr complex leading to LDLr degradation. Cholesteryl ester transfer protein (CETP) exchanges cholesteryl esters from LDL-P and HDL-P for TG from VLDL-P. In patients with metabolic syndrome and type 2 DM, VLDL-P is overloaded with TG, and CETP activity is increased. This leads to the formation of small, dense, cholesterol-poor LDL-Ps, which remain longer in the circulation. It also leads to the formation of small, unstable, cholesterol-poor HDL-P. ApoA1is lost in the urine leading to decreased HDL-C [2, 3].

Epidemiology

Western lifestyle increases the prevalence of dyslipidemia worldwide. In the USA, mean LDL-C levels decreased from 126.2 mg/ dL (1999–2000) to 111.3 mg/dL (2013–2014). The age-adjusted prevalence of high LDL-C (≥130 mg/dL) decreased from 42.9% (1999–2000) to 28.5% (2013–2014). Approximately 17% of adults (~25% of males and <10% of females) have low HDL-C. Approximately 25% of adults had high triglyceride levels (≥150 mg/dL) [4].

Screening for Dyslipidemias in Adults

The US Preventive Services Task Force (USPSTF) has abandoned previous recommendations of screening for dyslipidemia, replacing them with recommendations about statin use for the primary prevention of cardiovascular disease [5]. The 2018 ACC/AHA/Multisociety cholesterol guideline recommends lipid screening every 4–6 years with a fasting or nonfasting lipid panel. However, if abnormalities are identified and interventions are implemented, including lifestyle or drug therapy, lipid testing is endorsed every 4–12 weeks after each change and between 3 and 12 months once desired lipid levels are achieved [1].

Screening for Dyslipidemias in Children

USPSTF found insufficient evidence to recommend for or against routine screening for

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dyslipidemias in infants, children, and adolescents 20 years or younger [6]. The 2018 ACC/AHA/Multisociety cholesterol guideline states that in children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non-HDL-C once between the ages of 9 and 11 years and again between the ages of 17 and 21 years [1]. Moreover, in children and adolescents with a family history of either early CVD or significant hypercholesterolemia, the same guideline states that it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect familial hypercholesterolemia or rare forms of hypercholesterolemia [1].

Classification

Dyslipidemias can be divided into primary (genetic) and secondary.

Classic Fredrickson's classification distinguishes the following:

- *Type I (familial hyperchylomicronemia syndrome, FCS)*: TG to TC ratio ~10:1, TG >1,000 mg/dL; presentation often in children with abdominal pain (recurrent pancreatitis) and eruptive xanthomas. No elevated atherosclerotic cardiovascular disease (ASCVD) risk. Prevalence ~1:1,000,000. FCS phenotype is most often caused by homozygosity of the gene encoding LPL or several associated factors regulating its activity.
- *Type IIa (familial hypercholesterolemia, FH)*: LDL-C usually ≥190 mg/dL, in homozygous FH (HoFH) often up to 400 mg/dL and above. Subjects with mild mutations and heterozygous FH (HeFH) may have LDL-C <190 mg/dL. Early ASCVD, sometimes in children and adolescents. Tendon xanthomas and corneal arcus at age <45 are frequent findings. FH phenotype is classically caused by LDL receptor mutations but can be seen with mutations of ApoB, PCSK9 (gain of function), or LDLRAP1 (recessive). Prevalence HoFH 1:250,000, HeFH 1:250.
- *Type IIb (familial combined hyperlipidemia, FCH):* LDL-C, TG elevated, low HDL-C, TG to TC ratio ~5:1, atherogenic, frequent with metabolic syndrome. Prevalence ~1:100–1:200. Polygenic inheritance.
- *Type III (dysbetalipoproteinemia):* IDL-P and ChR elevated, TC ~300 mg/dL, TG ~300 mg/dL, tuberoeruptive xanthomas, orange palmar xanthomas, atherogenic. Caused by ApoE2/E2 genotype or rare ApoE mutations, often silent, unmasked by environmental factors in <20% of ApoE2/E2 homozygotes. Prevalence ~1:200.
- *Type IV (hypertriglyceridemia)*: TC ~250 mg/dL, TG 400–1,000 mg/dL, low atherogenicity, exacerbated by alcohol and poor diet. Prevalence ~1:100–1:200. Polygenic inheritance.
- *Type V (mixed hyperlipidemia)*: TC ~250 mg/dL, TG >1,000 mg/dL, both chylomicrons and VLDL-P elevated, can present in childhood similar to type I or later in life with type 2 DM, gout, and metabolic syndrome. Prevalence ~1:100–1:200. Polygenic inheritance.

Dyslipidemias not included in the Fredrickson classification:

- *Elevated lipoprotein (a)*: Lp(a) is a prothrombotic and atherogenic lipoprotein, with a specific Apo(a) covalently bound to ApoB, often found in families with early ASCVD. Twenty percent of US population has elevated Lp(a) >50 mg/dL, considered a risk-enhancing factor for ASCVD. The higher Lp(a) level, the higher the risk. Patients with high Lp(a) often develop aortic valvular disease in addition to CAD.
- *Inherited low HDL-C*: hypoalphalipoproteinemia is usually associated with increased ASCVD. Includes rare Tangier's disease and lecithin-cholesterol acyltransferase (LCAT) deficiency, which in its heterozygous form is known as fish-eye disease. Very rare forms of low HDL-C (ApoA1 Milano) are cardioprotective.
- *Inherited high HDL-C*: very high HDL-C levels (>100 mg/dL) are not cardioprotective,

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as they often reflect deficient function of HDL-P and are associated with atherosclerosis.

- *Inherited low LDL-C*: hypobetalipoproteinemia, autosomal dominant, ApoB deficiency, heterozygote patients have LDL-C <20 mg/dL, decreased ASCVD risk. Homozygote ApoB deficiency can present similarly to abetalipoproteinemia, which is autosomal recessive, microsomal transfer protein (MTP) deficiency presents in childhood (homozygotes only) with symptoms of deficiency of fat-soluble vitamins; LDL-C and VLDL-C are undetectable.
- *PCSK9 loss-of-function mutations*: loss-of-function PCSK9 mutations lead to moderate (heterozygous) LDL-C decrease (40–60 mg/dL) or more pronounced LDL-C (homozygous) decrease (~20 mg/dL) and are associated with decreased ASCVD risk, without any adverse effects.
- *Familial combined hypolipidemia*: autosomal recessive, ANGPTL3 mutations; all lipid levels are very low, including HDL-C; decreased ASCVD risk.
- *Sitosterolemia*: autosomal recessive, ABCG5/8 mutations, with or without elevated LDL-C, caused by accumulation of toxic plant stanols and sterols, normally not absorbed into systemic circulation, increased risk of ASCVD, tendon xanthomas. Prevalence ~1:1,000,000.
- *Cerebrotendinous xanthomatosis (CTX)*: rare, autosomal recessive, caused by CYP27A1 mutations, normal LDL-C levels, resulting from accumulation of cholestanol, increased ASCVD risk, mimics HoFH plus cataracts and neurological abnormalities. Prevalence ~1:50,000.
- *Cholesteryl ester storage disease, LAL (lysosomal acid lipase) deficiency*: high LDL-C and TG, very low HDL-C, elevated LFTs, unexplained hepatosplenomegaly and hepatosteatosis. *Wolman's disease* is caused by complete LAL absence, fatal ~1 year of age, due to anemia, liver failure, and cachexia. Prevalence ~1:50,000.

Secondary dyslipidemias can be subdivided by causative condition into lifestyle induced (high-cholesterol/high-fat diet, sedentary lifestyle, alcohol), endocrine (metabolic syndrome/DM, hypothyroidism, Cushing, polycystic ovarian syndrome), drug induced (cyclosporine, progestins, thiazides, beta-blockers, retinoids, estrogens, steroids, atypical antipsychotics, protease inhibitors), pregnancy, renal (chronic renal disease, nephrotic syndrome), infectious (HIV, hepatitis), hepatic (obstructive liver disease, cholestasis leading to buildup of lipoprotein X), storage disease (Gaucher's), and others (anorexia nervosa, cancer, transplant patients). Atherogenic dyslipidemia associated with metabolic syndrome, obesity, and/or type 2 DM is characterized by high TG, low HDL-C, and normal or only slightly elevated LDL-C. However, there is a significant increase in LDL-P, which can be measured directly by NMR or increased ApoB, which correlates better with increased ASCVD risk than LDL-C [1–3].

Diagnosis of Dyslipidemias

History

Patients with dyslipidemia often have signs and symptoms of atherosclerosis in different locations; therefore, it is important to inquire about exertional chest pain, history of abnormal EKG, stress test, intermittent claudication, erectile dysfunction, diagnosed CAD, or stroke/TIA. High TG level may cause recurrent pancreatitis in adults and children. History of intermittent abdominal pain and skin eruptions characterizes patients with FCS. Infants with hypo- and abetalipoproteinemia present with failure to thrive, steatorrhea, and developmental delay. Recurrent Achilles tendonitis in a child or adolescent may indicate FH. Family history should focus on premature ASCVD, early death, unusual skin/tendon lesions, pancreatitis, or known lipid disorders. It is important to review dietary habits, smoking history, alcohol use, exercise, and use of any medications or dietary supplements.

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Physical Examination

Many physical findings are present in patients with dyslipidemias. Excess cholesterol and/or TG form deposits in different tissues. *Xanthelasmas* are flat, demarcated cholesterol deposits in subcutaneous tissue usually in or close to eyelids. Xanthelasmas are common and nonspecific, often a familial trait unrelated to dyslipidemia, never related to TG elevation. Larger and more tuberous cholesterol deposits are called xanthomas. *Tendon xanthomas*, specifically Achilles tendon xanthomas, are found in FH, CTX, and sitosterolemia patients, often at an early age. *Tuberoeruptive xanthomas* on elbows and knees as well as *palmar xanthomas* are found in dysbetalipoproteinemia. *Arcus senilis* is a grayish/white C/phospholipid deposit in the corneal margin. When found at <45 years of age, it is associated with dyslipidemia; later in life is a nonspecific finding. Clouding of the entire cornea is a characteristic of fish-eye disease. *Eruptive xanthomas* are TG accumulations in the form of small papules often with an inflammatory base, found in hyperchylomicronemia. Fundoscopic eye exam in children suspected to have HoFH may reveal ischemic optic neuropathy. *Lipemia retinalis* is a creamy white appearance of retinal vessels associated with high TG levels. *Orange tonsils* are characteristic of Tangier's disease. Hepatosplenomegaly can be found in patients with type I or type V dyslipidemia, as well as with LAL deficiency. A systolic ejection murmur at the right upper sternal border can be auscultated in patients with HoFH or very high Lp(a) levels, reflecting aortic stenosis (AS) resulting from xanthomatous infiltration of aortic valves (valvular AS) and root (supravalvular AS). Patients with CTX show cataracts and various neurological symptoms: ataxia, dysarthria, dementia, and seizures [2, 7].

Laboratory and Imaging

It is important to distinguish measured C levels within lipoprotein particles (-C) from the actual levels of particles themselves (-P). LP provides information about TC, LDL-C, HDL-C, VLDL-C, as well as TG. Non-HDL-C is calculated by subtracting HDL-C from TC. When LP is collected, nonfasting TG levels can be 20–40% higher than fasting. When LDL-C is calculated by the Friedewald formula [LDL-C = TC− (HDL-C + TG/5)], it becomes inaccurate with TG >200 mg/dL and unreliable with >400 mg/dL. It is also inaccurate at low LDL-C (<70 mg/dl) and TG (≥150 mg/dL) levels. Therefore, in such cases calculation using the new Martin formula is preferred, or a direct LDL-C measurement should be obtained. Nonfasting samples can be used for risk assessment in primary prevention and for assessment of baseline LDL-C levels before the initiation of statin therapy in primary and secondary prevention. Checking TSH and UA for proteinuria will rule out two common secondary causes of dyslipidemia. Extent of preclinical atherosclerosis can be measured by three noninvasive methods: carotid intima-media thickness (CIMT), obtained by US; coronary calcium score (CACS), obtained by a limited CT scan; and screening coronary CT angiogram (CCTA) requiring iv contrast prior to CT. CIMT is no longer endorsed by major guidelines, but it is useful in younger populations. CACS has received full endorsement as a definite tool to demonstrate the presence of subclinical disease. CACS of zero allows reclassification of patients to low risk and withholding of statin therapy except in smokers and patients with diabetes and strong family history of heart disease [1].

Special Testing

Advanced lipid tests include combinations of measurements, obtained by different proprietary techniques. Caution is advised when using those tests, as many of them lack high-level evidence for their use, especially in the general population. An exception is ApoB and LDL-P level testing. LDL-C and LDL-P can be discordant in up to 30% of individuals, especially those with metabolic syndrome. LDL-P or ApoB is a better predictor of CV risk than LDL-C. ApoB ≥130 mg/dL corresponds to LDL-C ≥160 mg/dL and is

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considered a risk-enhancing factor. High-sensitivity HS-CRP evaluates for potential intravascular inflammation, considered as a risk-enhancing factor favoring statin therapy. Elevated Lp(a) levels ≥50 mg/dL or ≥125 nmol/L are considered another risk-enhancing factor. Relative indications for its measurement are family history of premature ASCVD or personal history of ASCVD not explained by major risk factors. Lp (a) increases ASCVD risk especially at higher levels. Evidence is lacking to use HDL and LDL subfractions as well as more comprehensive inflammatory panels. Genotyping ApoE helps diagnose dysbetalipoproteinemia (Apo E2/E2), and it can also disclose increased risk of Alzheimer's disease (ApoE4/E4). Cholestanol and sitosterol measurements evaluate the proportion of cholesterol from intestinal absorption vs. synthesis in order to potentially guide therapeutic decisions [1–3].

Differential Diagnosis

Treatable, secondary causes of dyslipidemia need to be ruled out before concluding that it is a primary, i.e., genetic, problem. Most cases of dyslipidemia reflect a combination of genetic and environmental factors.

Treatment

Mild dyslipidemias are often amenable to therapeutic lifestyle modifications (TLMs) which are the baseline of therapy for primary and secondary ASCVD prevention. However, pharmacologic therapy is often required. The 2018 ACC/AHA/Multisociety guideline algorithm for initiation of lipid-lowering therapy in secondary prevention is presented in Fig. 1. While statins remain the first-line therapeutic agents, an LDL-C threshold of ≥70 mg/dL is introduced to add ezetimibe and PCSK9 inhibitors. The primary prevention algorithm is presented in Fig. 2. Lipid-lowering therapy should be initiated without calculating risk in patients with LDL-C ≥190 mg/dL and patients aged 40–75 with DM and LDL-C 70–189 mg/dL. For patients with DM younger than 40, initiation of statin therapy is favored when they have one or more of the following risk enhancers: 1) long duration of DM (≥10 years for type 2 and ≥20 years for type 1); 2) albuminuria ≥30 mcg/mg creatinine; 3) eGFR <60 mL/min/1.73 m; 4) retinopathy; 5) neuropathy; and 6) ABI <0.9. For patients aged 40–75 and LDL-C 70–189 mg/dL, 10-year ASCVD should be calculated using pooled cohort equations [8]. For patients in low-risk category (<5%), no treatment is needed. For patients in the intermediate-risk category (≥7.5%– 20%) and selected patients in the borderline-risk category (5%–7.5%), initiation of moderate-intensity statin therapy is advised, especially if the presence of risk-enhancing factors (Fig. 2) favors initiation of statin therapy. In cases of doubt, obtaining CACS helps with the decision to initiate lipid-lowering therapy. For high-risk category (≥20%) initiation of high-intensity statin is advised [1]. Lipid-lowering therapy is a key component to a comprehensive approach for primary ASCVD prevention as outlined in a separate guideline [9]. The 2019 European lipid guideline has much more aggressive goals of lipid-lowering therapy than the 2018 ACC/AHA/Multisociety guideline, aiming for an LDL-C of ≤55 mg/dL for many patients and an LDL-C goal of ≤40 mg/dL for patients with recurrent events [10]. It should be kept in mind that there is not such thing as an LDL-C level being "too low," as the safety of very low LDL-C is well established and there is not an LDL-C level beyond which further reduction is not beneficial [11].

Moderate hypertriglyceridemia is an independent risk factor for ASCVD, while severe hypertriglyceridemia (fasting triglycerides ≥500 mg/) can lead to pancreatitis [12]. The 2018 ACC/AHA/Multisociety guideline emphasizes that in adults with severe hypertriglyceridemia and especially fasting triglycerides ≥1000 mg/dL, it is reasonable to identify and address other causes of hypertriglyceridemia and, if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty

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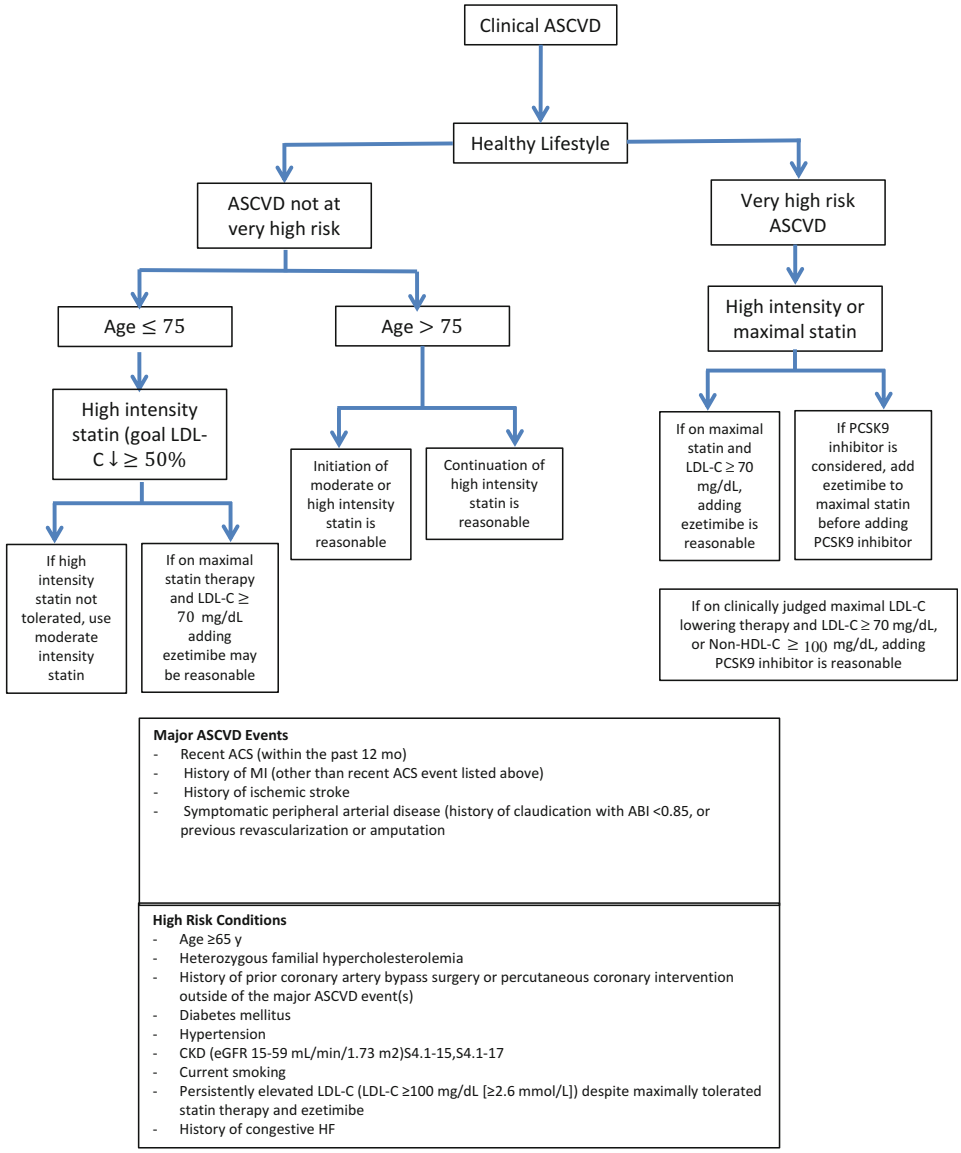


Fig. 1 Algorithm of major recommendations for lipid-lowering therapy for secondary ASCVD prevention based on 2018 ACC/AHA/Multisociety guideline. Heart-healthy lifestyle is the foundation for secondary prevention. In individuals not at very high risk, high-intensity statin therapy should be used, with addition of ezetimibe, if LDL-C remains above the 70 mg/dL threshold. In patients at very high risk, PCSK9 inhibitors should be added if LDL-C remains above the 70 mg/dL threshold and/or 100 mg/dL non-HDL-C threshold despite maximally tolerated statin±ezetimibe therapy. To determine whether a patient is at very high risk, they need to have a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions as listed in the table at the bottom of the figure

acids, and, if necessary to prevent acute pancreatitis, fibrate therapy. No recommendations are made to treat moderate hypertriglyceridemia (175–499 mg/dL), which is considered as a risk-enhancing factor alone and as part of the metabolic syndrome [1]. Recent data have shown treatment of patients with moderate hypertriglyceridemia and ASCVD or type 2 diabetes and several cardiovascular risk factors with 4 g daily of icosapent ethyl (pure EPA omega-3

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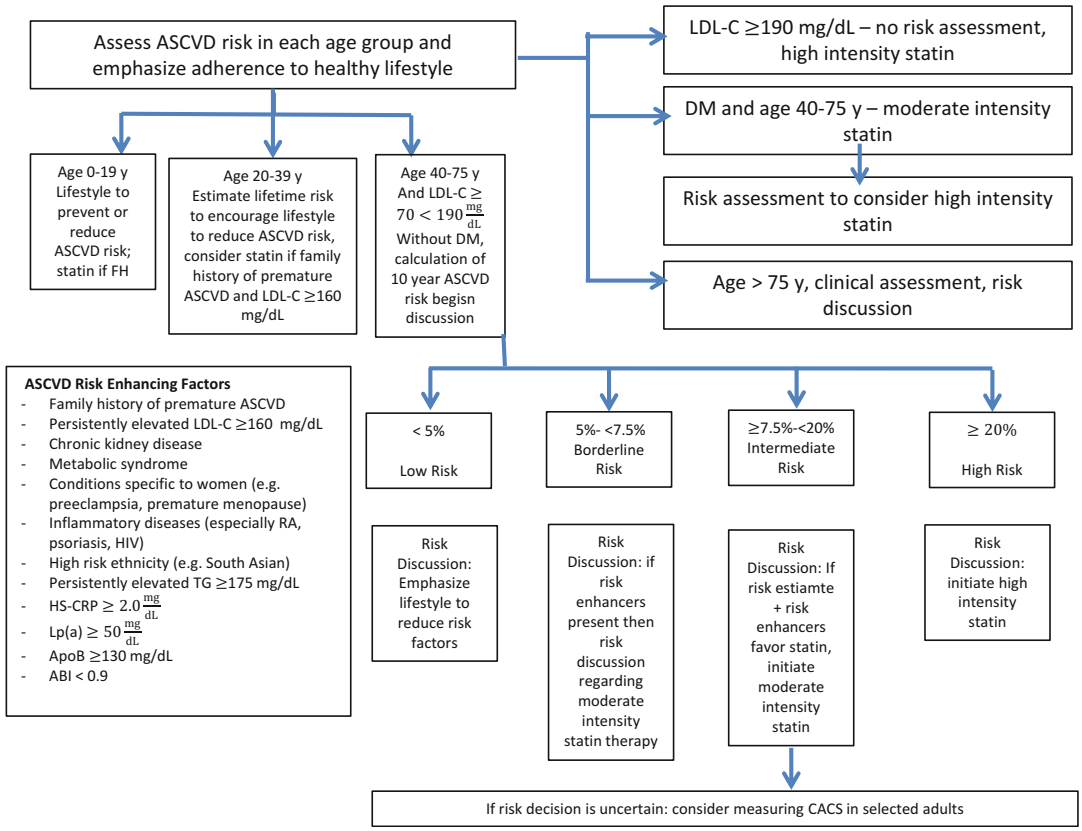


Fig. 2 Algorithm of major recommendations for lipid-lowering therapy for primary ASCVD prevention based on 2018 ACC/AHA/Multisociety guideline. Heart-healthy lifestyle is the foundation for prevention across all ages. Statin therapy should be initiated through a shared decision-making process in a patient-centric manner. Inclusion of risk-enhancing factors allows for an individualized approach therapy. CACS allows for detection of subclinical coronary artery disease to help guide clinical decisions

preparation) leads to a 25% reduction of cardiovascular events with a NNT of 21 [13]. This recommendation has been incorporated into the newest European guideline [10]. In contrast to high TG, low HDL-C should be used only as a marker of cardiovascular risk but not as a target of therapy [1].

Medications

There are various classes of drugs used to treat dyslipidemias (Table 1), with several new drugs in development [14]. LDL-C lowering by each 38.4 mg/dL (1 mmol/L) leads to a roughly 23% reduction in cardiovascular events for both primary and secondary prevention as demonstrated in many clinical trials, mostly involving statin therapy but also other interventions including PCSK9 inhibitors and ezetimibe. Statins inhibit hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol synthesis. This leads to increased removal of LDL-P from plasma by LDLr upregulation in the liver. Statins decrease LDL-C (18–55% reduction), non-HDL-C (15–51%), and TG (7–30%) while increasing HDL-C (5–15%). Bempedoic acid reduces LDL-C by ~18% through inhibiting ATP citrate lyase, an enzyme upstream of HMG-CoA reductase. However, its place in therapy remains unclear, until results of the cardiovascular outcome trial become available. Removing PCSK9 by the use of monoclonal antibodies (evolocumab and alirocumab) allows recycling

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Table 1 Lipid-lowering medications

Medication	Dose range	LDL reduction (%)	Cost	Side effects and special considerations	Pregnancy category
Statins (HMG-CoA reductase inhibitors)					
Atorvastatin (Lipitor)	10 mg qd min 80 mg qd max	31–35 50–60	$	CYP3A4 metabolized, long half-life, avoid erythromycin, azoles, protease inhibitors, cyclosporine, and grapefruit juice	X
Rosuvastatin (Crestor)	5 mg qd min 40 mg qd max	40–48 58–64	$–$$	Minimal CYP2C9, long half-life	X
Fluvastatin (Lescol)	20 mg qhs min 80 mg XL max	20–25 27–32	$$	CYP2C9, least chance of myopathy, short half-life	X
Lovastatin (Mevacor)	10 mg qhs min 80 mg qhs or 40 mg bid max	25–30 35–40	$	CYP3A4 metabolized, short half-life, avoid erythromycin, azoles, protease inhibitors, cyclosporine, and grapefruit juice. Best absorbed with food	X
Pitavastatin (Livalo, Zypitamag)	1 mg qd 4 mg qd	32–46	$$$	Minimal CYP2C9 and 2C8, long half-life	X
Pravastatin (Pravachol)	10 mg qhs min 80 mg qhs max	25–32 17–32	$	Minimal CYP metabolism, short half-life, avoid erythromycin	X
Simvastatin (Zocor)	10 mg qhs min 40 mg qhs max	27–32 38–43	$	CYP3A4 metabolized, short half-life, avoid erythromycin, azoles, protease inhibitors, cyclosporine, and grapefruit juice. Decrease dosing of diltiazem, verapamil, amlodipine, and amiodarone	X
Cholesterol absorption inhibitors					
Ezetimibe (Zetia)	10 mg qd	17–22	$–$$	Well tolerated; when combined with statin, it can raise LFTs and contribute to myalgia/myopathy. Available in combination with simvastatin (Vytorin) and atorvastatin (Liptruzet)	C
ATP citrate lyase inhibitors					
Bempedoic acid (Nexletol)	180 mg qd	15–24	$$$	Well tolerated in statin-intolerant patients, can induce gout and tendon rupture, in combination with ezetimibe lowers LDL-C by 48%	?
Bile acid sequestrants					
Colestipol (Colestid)	2–16 g qd or divided (start low and titrate up)	10–25	$$	Do not use when TG >300; constipation; decreased absorption of many drugs and vitamins. Contraindicated when hx of bowel obstruction	B
Cholestyramine (Questran)	4–16 g divided bid (start low and titrate up)	10–25	$$	Do not use when TG >300; constipation; decreased absorption of many drugs and vitamins. Contraindicated when hx of bowel obstruction	C

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Table 1 (continued)

Medication	Dose range	LDL reduction (%)	Cost	Side effects and special considerations	Pregnancy category
Colesevelam (Welchol)	3.75 g qd or divided bid	10–25	$$$	Easier to use, less interactions. Do not use when TG >300; constipation; decreased absorption of many drugs and vitamins. Lowers A1C 0.5%. Contraindicated when hx of bowel obstruction	B
Niacin (nicotinic acid – not nicotinamide)					
Niacin immediate release, crystalline (Niacor, etc.)	100–3,000 mg initial dose qd, then divided bid/tid, titrate up slowly	5–25	$	Flushing, dry skin, rash, glucose intolerance/new-onset type 2 DM, hyperuricemia, dyspepsia/PUD, afib, infections. May enhance side effects of statins	C
Niacin sustained release (Endur-Acin, etc.)	500–2,000 mg qhs, titrate up slowly	5–25	$	Flushing, dry skin, rash, glucose intolerance/new-onset type 2 DM, hyperuricemia, dyspepsia/PUD, afib, infections. May enhance side effects of statins. Monitor LFTs due to potential hepatotoxicity	C
Niacin extended release (Niaspan)	500–2,000 mg qhs, titrate up slowly	5–25	$$–$$$	Flushing, dry skin, rash, glucose intolerance/new-onset type 2 DM, hyperuricemia, dyspepsia/PUD, afib, infections. May enhance side effects of statins. Monitor LFTs due to potential hepatotoxicity	C
Fibrates					
Gemfibrozil (Lopid)	600 mg bid	6–20 when TF <400, increase when TG >400	$$	Avoid combination with statins due to increased risk of myalgia/myopathy	C
Fenofibrate (Tricor, Trilipix, Lofibra, Fenoglide, Lipofen, Triglide, etc.)	43–200 mg qd	6–20 when TF <400, increase when TG >400	$–$$$	May be combined with statins. Avoid in kidney disease. Multiple formulations make dosing confusing	C
Pemafibrate (Parmodia)	0.1–0.2 mg BID	Lowers TG, raises HDL-C and LDL-C	$$$?	Approved in Japan, awaiting US approval	
ω3 polyunsaturated fatty acids					
DHA/EPA (Lovaza)	4 g qd or 2 g BID	Increase up to 40%	$–$$	Well tolerated,, may increase bleeding time, no cardiovascualr outcomes	C
EPA (Vascepa)	2 g BID	0	$$$$	25% of MACE RRR with 21 NNT Well tolerated, may increase bleeding time	C

(continued)

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Table 1 (continued)

Medication	Dose range	LDL reduction (%)	Cost	Side effects and special considerations	Pregnancy category
Microsomal triglyceride transfer protein inhibitors					
Lomitapide (Juxtapid)	Start 5 mg qd, titrate up as tolerated up to 60 mg qd	40–50	$$$$$$$	Use restricted to HoFH, REMS required; risk of hepatotoxicity. Requires strict low-fat diet. GI side effects	X
ApoB antisense oligonucleotide					
Mipomersen (Kynamro)	200 mg Subq injection, q week	40–50	$$$$$$$	Use restricted to HoFH, REMS required; risk of hepatotoxicity; currently not available on the market	B
PCSK9 inhibitor antibodies					
Alirocumab (Praluent)	75 or 150 mg Q14 days or 300 mg q 30 days; sc injection	45–50%	$$–$$$	Very well tolerated, ~15% RRR of cardiovascular events (ODYSSEY OUTCOMES) Can lower Lp(a) 20–30%	Not assigned
Evolocumab (Repatha)	140 mg Q14 days or 420 mg Q30 days; sc injection	59–63%	$$–$$$	Very well tolerated, ~15% RRR of cardiovascular events (FOURIER) Can lower Lp (a) 20–30%	Not assigned
PCSK9 RNA interfering nucleic acid					
Inclisiran	300 mg Q 6 months; sc injection	53–58%	$$$$?	Very well tolerated, no significant side effects; convenience of 2 × year administration in clinician's office	?

of more LDLr to hepatocyte surface and thus for more efficient LDL-P removal from circulation, leading to a dramatic 50–60% LDL-C reduction on top of statins. Finally, ezetimibe blocks both intestinal and biliary cholesterol absorption and thus delivery to hepatocytes, leading to LDLr upregulation in the liver and a modest ~20% LDL-C decrease.

Statins are well tolerated, but up to 10% of patients may show statin intolerance, with many more showing statin aversion due to negative social media profile of this drug category. Myalgias and myopathy are the main reason of switching statin, nonadherence, and discontinuation of therapy. Severe rhabdomyolysis is very rare (1:100,000). However, patients initiating statins should be warned of signs and symptoms of this adverse reaction (tea-colored urine, oliguria, severe muscle pain, nausea, vomiting, confusion). Following liver function tests (LFTs) is no longer recommended in asymptomatic patients after the initiation of statin therapy. Mild elevation of LFTs (<3 × upper limit of normal) is observed in 1–2% of patients taking statins and should not lead to discontinuation of therapy. Statins confer a small, dose-dependent risk of developing type 2 DM in predisposed individuals (up to 9–12%). However, CV benefits from their use greatly outweigh this risk. While data from RCTs do not show any adverse effects of statins on cognition, several observational studies reported memory problems and cognitive impairments with statin use, which lead to their discontinuation. Ezetimibe is very well tolerated without major side effects. The same is true for injectable PCSK9 inhibitors, whose main side effects are injection site reactions and short-lasting flu-like symptoms seen in a minority of patients [11].

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LDL Apheresis

In severe FH multiple drugs are often used to achieve the therapeutic LDL-C goal. When maximally tolerated pharmacotherapy fails in selected patients (HoFH with LDL-C >500 mg/dL, HeFH and LDL-C >300 mg/dL, HeFH with LDL-C ≥100 mg/dL, and coronary artery disease), they can be treated with LDL apheresis. The procedure lasts 2–4 h and it is performed every 2–4 weeks in special facilities. Each apheresis session leads to a 49–75% decrease in LDL-C levels [15].

Nutraceuticals

Nutraceuticals are very useful in statin-intolerant patients and in patients preferring natural therapies. A combination of nutraceuticals may lead to a significant up to 50% LDL-C lowering. Red yeast rice contains natural lovastatin (2–10 mg), lowers LDL-C by ~27%, and decreases cardiovascular and total mortality by 30% and 33%, respectively. Other agents with significant LDL-C lowering but unproven cardiovascular outcomes include phytosterols, soluble dietary fiber, berberine, bergamot, artichoke, and soy products. There is no solid evidence supporting the use of garlic, guggulipid, policosanol, or tocotrienols in lowering LDL-C. Over-the-counter fish oil (ω3PUFA) lowers TG and LDL-P while raising HDL-C and LDL-C [16]. Statins lower CoQ10 levels; therefore, CoQ10 supplementation may prevent myalgias associated with statin use. However, CoQ10 use is not endorsed by the 2018 ACC/AHA/Multisociety guideline [1].

Referrals

Difficult-to-manage patients with dyslipidemias, especially patients with extreme LDL-C and TG elevations, requiring drugs beyond statins and ezetimibe, and those who do not respond appropriately to therapy should be referred to lipid specialists often practicing within specialized lipid clinics or preventive cardiology groups. Clinical lipidology is an emerging subspecialty open to family physicians [17].

Prevention

Therapeutic lifestyle modifications constitute the foundation of management of dyslipidemias. Adults should engage in at least 150 min per week of accumulated moderate-intensity or 75 min per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk. Diets high in saturated fats raise LDL-C and HDL-C. In addition, trans fats increase Lp(a) levels. High-carbohydrate low-fat diets lower LDL-C and HDL-C but increase TG and LDL-P and therefore should be avoided by patients with metabolic syndrome/type 2 DM. Mediterranean diet decreases LDL-C and raises HDL-C. Nut consumption decreases LDL-C and TG. Alcohol consumption raises TG and HDL-C. Patients with severe hypertriglyceridemia require very low-fat diets to prevent recurrent pancreatitis [1, 9].

Family and Community Issues

Cascade screening of family members is advised, especially in the case of FH and elevated Lp (a) [1]. Prevalence of FH is elevated in some ethnic groups (French Canadians, Ashkenazi Jews, Afrikaners, Lebanese Christians). The FH Foundation provides resources, support, and cascade registry [18]. The Lipoprotein (a) Foundation provides resources and support for patients with high Lp(a) [19]. Patients with FCS can find support and resources with the FCS Foundation [20].

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Diabetes Mellitus

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Nadine El Asmar, Baha M. Arafah, and Charles Kent Smith

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Definition

Diabetes mellitus is a group of diseases characterized by hyperglycemia and other metabolic abnormalities resulting from impaired insulin secretion and/or its action at the cellular level.

Epidemiology

Data from 2018 estimated that 10.5% of the US population or 34.2 million Americans had diabetes. Nearly 1.6 million have type 1 diabetes. A total of 1.5 million Americans are diagnosed with diabetes every year. In 2015, 88 million Americans age 18 and older had prediabetes. As the epidemic of obesity in the USA continues to be on the rise, diabetes in youth younger than 20 has followed. In 2014–2015, the annual incidence of diagnosed diabetes in youth was estimated at 18,200 with type 1 diabetes, 5800 with type 2 diabetes [1, 2]. Diabetes is a major risk factor for kidney failure as well as cardiovascular and cerebrovascular disease.

Classification

- Type 1 diabetes mellitus (insulin-dependent DM) is characterized by deficiency of insulin secretion due to autoimmune pancreatic beta-cell destruction.
- Type 2 diabetes mellitus (noninsulin-dependent DM) is usually part of the metabolic syndrome, which is associated with hypertension, dyslipidemia, and obesity. It is characterized by insulin resistance in addition to relative insulin deficiency.
- Latent autoimmune diabetes of adulthood (LADA) has a similar pathophysiology to type 1 DM but occurs in adults.

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- Maturity onset diabetes of the young (MODY) is a monogenic diabetes which is characterized by the onset of hyperglycemia at an early age but is not characteristic of type 1 diabetes. It is autosomal dominant in inheritance.
- Gestational diabetes is the development of new onset diabetes during pregnancy, usually during the third trimester.
- Secondary diabetes occurs as a result of either medications such as glucocorticoids, diseases of the pancreas such as cystic fibrosis or pancreatitis, or as a result of a surgical intervention such as a pancreatectomy. Secondary diabetes can also be frequently observed in patients with specific illnesses such as acromegaly, Cushing's syndrome, and pheochromocytoma.

On the other hand, type 2 diabetes accounts for 90–95% of all diabetes. The risk of developing type 2 diabetes mellitus increases with age typically >45. However, given the increased incidence of obesity, there has been an increasing incidence of type 2 diabetes at an age < 45. In type 2 diabetes, there is a progressive loss of adequate B-cell insulin secretion frequently on the background of insulin resistance [3]. Patients with type 2 diabetes mellitus are typically obese. They often present with polyuria, polydipsia, polyphagia, and at times unexplained weight loss. They are also often diagnosed on routine lab testing and screening employed to detect type 2 diabetes onset in patients with risk factors.

Diagnosis of Diabetes Mellitus

The biochemical diagnosis of diabetes mellitus is based on criteria established by the American Diabetes Association. These are listed in Table 1. Patients with type 1 diabetes can also present in an incidental manner on routine testing. Clues to diagnosis include age of onset and the presence of positive antibodies. Table 2 depicts the stages prior to the clinical development of type 1 diabetes.

LADA is characterized by slowly progressive autoimmune diabetes with an adult onset usually above 35 years of age. There is slow autoimmune B-cell destruction that indicates there may be a long duration of marginal and insufficient insulin secretion.

Table 1 Diagnostic criteria for diabetes mellitus and prediabetes

Diabetes mellitus	Prediabetes
1. Fasting blood glucose ≥126 mg/dl	1. Fasting blood glucose 100–125 mg/dl
2. 2 h post prandial glucose ≥200 mg/dl during an OGTT (using 75 g of an oral glucose load)	2. 2 h post prandial glucose 140–199 mg/dl during an OGTT
3. HbA1c of ≥6.5%	3. HbA1c of 5.7–6.4%
4. Random glucose of ≥200 mg/dl along with classic symptoms of hyperglycemia	
Diagnosis requires 2 abnormal test results from the same sample or in 2 separate test samples	

Adapted from the ADA 2020 guidelines

Table 2 Stages of type 1 diabetes

Stages of type 1 diabetes	Stage 1	Stage 2	Stage 3
Characteristics	– Autoimmunity – Normoglycemia – Presymptomatic	– Autoimmunity – Dysglycemia – Presymptomatic	– New-onset hyperglycemia – Symptomatic
Diagnostic criteria	– Antibody Positivity – No IFG or IGT	– Antibody positivity – Dysglycemia: IFG, IGT, and/or elevated HbA1c	– Clinical symptoms – Diabetes by standard criteria

IFG (impaired fasting glucose): Fasting plasma glucose 100–125 mg/dl
IGT (impaired glucose tolerance): 2 h postprandial glucose 140–199 mg/dl
HbA1c: 5.7–6.4%

Adapted from the ADA 2020 guidelines

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Of note, the traditional paradigms of type 2 diabetes occurring only in adults and type 1 diabetes only in children are no longer accurate, as both diseases occur in most age groups.

Diabetes is usually preceded by the prediabetes stage which is characterized by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Prediabetes should not be viewed as an independent clinical entity but rather as an increased risk for diabetes and cardiovascular disease (CVD). Prediabetes is also associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension [3].

Important Aspects in Managing Patients with Type 1 DM

Optimal management of patients with type 1 DM requires a comprehensive and detailed overview of many aspects of the disease process. These include the following: insulin therapy, nutritional guidance, education, prevention of diabetic ketoacidosis (DKA), addressing other comorbidities such as smoking, hyperlipidemia, and hypertension. These will be addressed in some detail in the following sections. It is important to emphasize that insulin therapy is essential for the survival of patients with type 1 DM since this is an insulin-deficient state. That is, insulin therapy should never be interrupted and should be offered in different formulation that ensures the presence of insulin in the body at all times.

Management of Type 1 Diabetes: Insulin Considerations

The Diabetes Control and Complications Trial (DCCT) which was one of the biggest diabetes trials conducted on thousands of type 1 diabetics, demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes [4]. Lower A1C with intensive control (HbA1c of 7%) led to 50% reductions in microvascular complications over 6 years of treatment. At the time of its publication, the DCCT study did not show any macrovascular benefit nor any impact on mortality. Importantly, however, when patients enrolled in the DCCT study were followed for longer periods of time (EDIC study), the initial microvascular disease benefit persisted while there was also a demonstration of subsequent macrovascular benefit [5]. The UKPDS study (performed on thousands of type 2 diabetic patients) along with many other large trials also showed a consistent reduction in microvascular complications with implementation of intensive control; but failed to show a significant reduction in macrovascular complications or mortality (Table 1) [6]. Other studies that examined the impact of intensive insulin therapy in patients with type 1 diabetes showed a reduction in microvascular disease complications. The latter studies include the ACCORD, ADVANCE, and the VADT. It is of interest to note that none of the latter studies demonstrated reductions in macrovascular disease. As one can predict, there was an increase in the incidence of hypoglycemia among patients receiving more intensive insulin therapy.

Of note, the DCCT study was carried with human insulins (NPH and Regular) which result in greater incidence of hypoglycemia due to their pharmacokinetics [4]. Over the last 25 years, rapid-acting and long-acting insulin analogs have been developed that have distinct pharmacokinetics compared with recombinant human insulin: basal insulin analogs have longer duration of action with flatter, more constant plasma concentrations than NPH insulin; rapid-acting analogs (RAA) have a quicker onset and peak and shorter duration of action than regular human insulin.

For individuals with type 1 diabetes, intensive flexible insulin therapy education programs using the carbohydrate counting meal planning approach results in improved glycemic control [7]. Patients should be trained to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. Typical multidose regimens for patients with type 1 diabetes combine premeal use of shorter-acting insulins with a longer acting formulation, usually at night.

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Table 3 Insulin pharmacokinetics

Insulin	Name	Onset of action	Peak	Duration
Rapid acting analogs	Lispro Glulisine Aspart	5–15 min	1 h	3–4 h
Short acting	Human regular	30 min	2–4 h	6–8 h
Intermediate acting	Human NPH	1–3 h	4–8 h	12–16 h
Concentrated human regular insulin	U-500 human regular insulin	1–3 h	4–8 h	Up to 24 h
Basal analogs	Glargine Detemir Degludec	2 h 2 h 1 h	No distinct peak No distinct peak No peak	20–24 h 12–24 h 42 h
Premixed insulin products	NPH/regular 70/30 NPH/Lispro 75/25 NPH/Aspart 70/30	Kinetics reflect individual components		

The pharmacokinetics of different types of insulin preparations are shown in Table 3 [8].

The rational for having a long-acting insulin is to ensure that insulin is available throughout the day and night. This can be achieved by using a single dose of glargine insulin, for example, or two doses of NPH insulin. Long-acting basal dose is titrated to regulate overnight, fasting glucose. Postprandial glucose excursions are best controlled by a well-timed injection of prandial insulin. The optimal time to administer prandial insulin varies, based on the pharmacokinetics of the formulation (regular, RAA, inhaled). Recommendations for prandial insulin dose administration should therefore be individualized. Typically, RAA should be injected up to 10 min before meals, while regular insulin should be administered 30 min prior to meals to optimize post prandial glycemic control. In general, patients with type 1 diabetes require 50% of their daily insulin as basal and 50% as prandial. Total daily insulin requirements can be estimated based on weight, with typical doses ranging from 0.4 to 1.0 units/kg/day. Higher amounts are required during puberty, pregnancy, and medical illness [7].

An example of a typical type 1 diabetes regimen is the following:

Lantus (glargine) 10 units at bedtime and Humalog (lispro) before meals according to a 1:15 g carb ratio. If 45 g of carbs are consumed with a meal, then 3 units of Humalog must be administered prior to the meal, in addition to a correction factor (or sensitivity factor). For example, one unit must be added for every 50 mg/dl above 150. So, if the premeal blood sugar is 162 mg/dl, the patient should administer 3 + 1 = 4 units of Humalog prior to that meal. The correction factor (also commonly known as sliding scale) can be modified based on insulin sensitivity, individualized glucose goals, and hypoglycemia risk.

Insulin Delivery Systems

Most patients with diabetes use insulin in the form of vials or pens. Inhaled insulin is also available. Certain insulins, however, are available in strictly vial or pen forms. When choosing the best delivery method, factors such as patient preference and cost should be taken into consideration. The typical syringe sizes used to draw insulin from the vials are 1 ml which allows up to 100 units, 0.5 ml (50 units), and 0.3 ml (30 units) of U-100 insulin at a concentration of 100 unit/ml. U-500 insulin vials and pens are also available at a concentration of 500 units per ml. Syringes are typically used once. In patients with dexterity issues or vision impairment, insulin pens should be considered for the administration of accurate doses. Pens are available with prefilled cartridges or reusable insulin pens with replaceable cartridges. Pens also vary with respect to dosing increment which

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can range from half-unit doses to 2-unit dose increments. Needles thickness and length should also be taken into consideration with higher gauge indicating thinner needles (22–33) which typically cause less pain. Length varies from 4 mm to 12.7 mm with shorter needles decreasing the risk of intramuscular injections.

Insulin pumps or automated insulin delivery are also available and should be reserved for use for competent patients with good self-management capabilities. These have integrated dose calculators which aid in decision-making with regards to titrating insulin doses. Another available delivery system is a patch-like disposable device which is changed on a daily basis and provides a continuous infusion of rapid acting as basal insulin and, at the same time, allows bolus increments for meals by simply pressing a button [9].

Insulin Injection Technique

While administering insulin, care must be taken to inject into subcutaneous tissue, not intramuscularly. The recommended sites for insulin injection include the abdomen, thigh, buttock, and upper arm.

Lipohypertrophy, which is an accumulation of subcutaneous fat in response to the adipogenic actions of insulin, can occur at a site of multiple injections. Therefore, it is necessary to remind patients to rotate injection sites to avoid this complication which can result in erratic insulin absorption. On exam, lipohypertrophy appears as soft, smooth raised areas which can potentially result in unexplained hypoglycemic episodes.

Patients and/or caregivers should receive education about proper injection site rotation. Finally, health-care providers must also routinely examine the injection sites and evaluate injection techniques as part of a comprehensive diabetes evaluation.

Diabetes Education and Self-Management

This is certainly one of the cornerstones of the management of diabetes. Patients with diabetes 1 or type 2 require education on making the proper food choices and identifying carbohydrate-containing foods. It is crucial to have an initial nutrition visit and regular nutrition follow-up to learn how to read food labels and assess carbohydrate content especially when insulin is required for blood glucose control, as inappropriate administration may result in hypoglycemia. In addition, patients need to be educated on self-monitoring of blood glucose. Instruction of patients in self-titration of insulin doses based on self-monitoring of blood glucose improves glycemic control in patients with type 2 diabetes initiating insulin. In patients with type 1 or 2 diabetes on multiple daily injections, home blood glucose levels should be checked prior to meals and snacks and at bedtime, prior to exercise, when hypoglycemia is suspected, after hypoglycemia treatment and prior to driving, in patients on multiple daily injections or subcutaneous insulin pump.

Another important aspect of self-monitoring of type 1 diabetes is ketone testing. Ketone testing is also important in the management of pregnant patients with diabetes since they are at higher risk to develop ketonemia and diabetic ketoacidosis. Patients should use these strips during illness, when the blood glucose is persistently >300 mg/dl, or when symptoms of nausea, vomiting, or abdominal pain are present. Their presence may indicate DKA and which can in some mild cases be managed at home with increased water intake, administration of insulin every 4 h, and monitoring of symptoms. Medical attention should be sought when symptoms do not improve. Of note, widely available urine home ketone testing strips do not detect beta-hydroxybutyrate, which is the predominant ketone, and may miss cases of DKA. Home blood beta-hydroxybutyrate strips are also available [10].

Glucose Monitoring Devices/Diabetes Technology

Technological advances over the past 25 years had a major impact on diabetes management. The advances introduced newer methods to monitor glucose and others to synchronize insulin administration as illustrated in Fig. 1. Glucose meters

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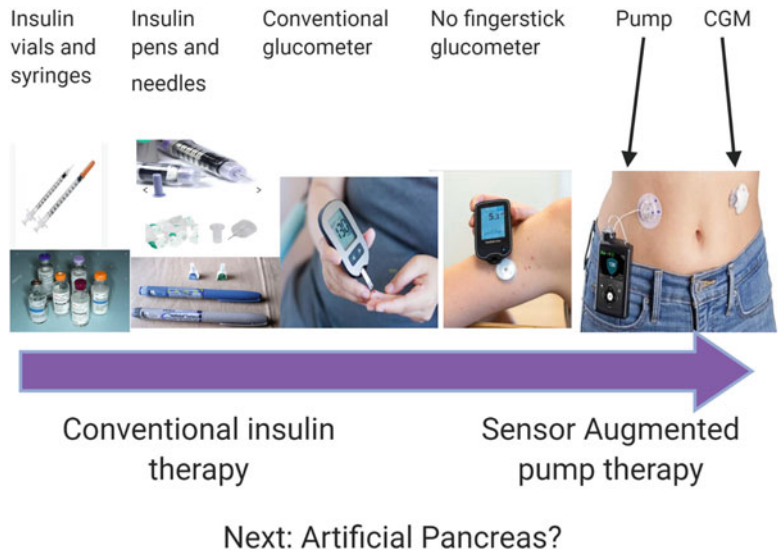


Fig. 1 Historical advancement of glucose monitoring and insulin delivery

that meet the FDA requirements for meter accuracy provide the most accurate data for diabetes management. These meters utilize an enzymatic reaction linked to an electrochemical reaction, either glucose oxidase or glucose dehydrogenase. The ones based on glucose oxidase can be falsely low in the setting of high oxygen tension and falsely high in the setting of hypoxia. If there is a discordance between the meter reading and clinical reality, then the reading must be retested in a lab. The FDA standards expects glucose meters for home use to have a 95% accuracy within 15% for all blood glucose in the usable range (numeric readings other than low, high, or error) and a 99% accuracy within 20%. According to the international Organization for Standardization (ISO) which is the reference organization in Europe, readings should be 95% within 15% for blood glucose of $\geq$100 mg/dl or 95% within 15 mg/dl for blood glucose of $<$100 mg/dl. The Diabetes Technology Society Blood Glucose Monitoring System Surveillance Program provides information on the performance of devices used for self-monitoring of blood glucose.

The meter supplies include strips and lancets. Patients should wash their hands before every blood glucose check. The lancet is then used to prick at the side of the fingertips and a drop of blood should be placed on a strip which is then inserted in the glucose monitor. In few seconds, a glucose reading should appear on the meter. A liquid control solution may be used to check for the glucometer's accuracy. Patients should be advised to purchase meters from pharmacies and avoid purchasing strips or supplies not authorized for sale in the USA. Patients should be advised against purchasing or reselling second-hand test strips, or using expired strips as these may give incorrect results [9]. In addition, strips must be stored in their sealed containers, away from direct light or humidity, and at room temperature.

Diabetes technology involves the devices, software, and hardware used to manage diabetes. It includes delivery systems such as insulin pumps, pens, and syringes as well as continuous glucose monitors (CGM) devices and glucose meters. Newer forms of diabetes technology include hybrid devices that both deliver insulin and monitor glucose levels and software that provides diabetes self-management support. Patients' interest in the use of diabetes technology in the primary care setting has greatly increased. The use of this technology should be individualized based on a patient's needs, desires, skill level, cost, and availability of devices.

There are two types of CGMs: real-time CGMs (for example, Dexcom G6 and Medtronic Guardian Sensor) measure glucose continuously and provide the user-automated alarms and alerts at specific glucose levels, for example, when high or low;

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while intermittently scanned CGMs (such as the freestyle libre device) only display glucose when swiped by a reader or a smart phone. Real-time and intermittently scanned CGM in conjunction with insulin therapy are useful tools to lower A1C and/or reduce hypoglycemia in adults with type 2 diabetes who are not meeting glycemic targets. The use of real-time CGM in adults with type 1 diabetes on either subcutaneous pump therapy or multiple daily injections is supported by data showing reduction in both hypoglycemia and A1C [9].

Insulin pump therapy should be considered in all adults and children with type 1 diabetes as long as they are able to manage the pump safely. It may also be considered in certain type 2 diabetic patients. Previous trials have demonstrated modest HbA1c lowering benefits when compared to multiple daily injection regimens in addition to reducing severe hypoglycemia episodes. In addition, in the last few years, the advent of sensor-augmented pump therapy has shown a significant reduction in hypoglycemia. Their use also may be considered to improve glycemic control. These systems increase and decrease insulin delivery based on sensor-derived glucose levels. They also have the ability to suspend insulin delivery if the blood glucose is low or predicted to become low in the next 30 min [9]. These systems, which fall under the artificial pancreas technology, are considered hybrid closed loop systems where basal insulin delivery is automated based on sensor glucose readings. However, the user would still need to manually input carbohydrates for meal boluses. The future of this technology might be a fully automated closed loop system with insulin only or with insulin and glucagon, which does not require any programming by the user.

Sick Day Management of Insulin

Improved education regarding sick day management is paramount, which includes the following:

1. Early contact with the health care provider.
2. Emphasizing the importance of continuing insulin therapy during an illness and the reasons not to discontinue without contacting the health-care team.
3. Periodic and frequent checking of blood glucose and review of goals and the use of supplemental short- or rapid-acting insulin.
4. Having medications and supplies at home to treat and monitor fever.
5. Increase intake of fluids and promoting ingestion of an easily digestible liquid diet containing carbohydrates and salt when nauseated.
6. Education of family members to help with following up on temperature, blood glucose, and urine/blood ketone testing; insulin administration; oral intake; and weight monitoring.

The use of home ketone testing along with glucose monitoring may allow early recognition of impending ketoacidosis, which may help to guide insulin therapy at home and, possibly, may prevent hospitalization for DKA.

Dawn Phenomenon

The dawn phenomenon is marked early morning elevation in blood glucose levels which results from a surge in counterregulatory hormone concentrations (growth hormone, cortisol, and catecholamines) in the absence of nocturnal hypoglycemia [8]. Delaying nighttime basal insulin might help with these early morning rises, however, continuous sensor-augmented pump therapy might offer a particular benefit since the nighttime/early am insulin rates can be adjusted to control the hyperglycemia.

Somogyi Phenomenon

The Somogyi phenomenon is post hypoglycemia (resulting from insulin therapy) hyperglycemia due to a surge in counterregulatory hormones, rather than overtreatment of hypoglycemia with excess carbohydrates [8]. Glucose sensor trends can provide insight into this phenomenon. Avoidance of hypoglycemia is important.

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Hypoglycemia

Hypoglycemia is typically precipitated in patients on secretagogues and patients on insulin therapy. According to the American Diabetes Association (ADA) , the definition of hypoglycemia in the diabetic patient is a glucose level of less than 70 mg/dl, which is considered a level 1. A level 2 hypoglycemia is <54 mg/dl. Level 3 is a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Patients should be assessed at every visit for symptomatic and asymptomatic hypoglycemia including assessment of frequency of occurrence. Hypoglycemia unawareness must always be taken into consideration. Patient who develop this condition should be advised to raise their glycemic targets in order to reverse hypoglycemia unawareness. Glucose (15–20 g) in the form of chewable tablets is the preferred treatment for the conscious individual with blood glucose <70 mg/dL [3.9 mmol/L]), although any form of carbohydrate that contains glucose may be used (4 oz. of orange juice). Fifteen minutes after treatment, if blood glucose shows continued hypoglycemia, the treatment should be repeated until blood glucose is normalized. Glucagon, in an injectable form, should also be prescribed for all individuals at increased risk of level 2 hypoglycemia, so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Recently, the FDA has approved intranasal glucagon (Baqsimi) which has facilitated the administration of this medication.

Pregnancy Planning

The majority of cases of diabetes in pregnancy are caused by gestational diabetes which typically develops during the third trimester of pregnancy. The remaining cases are attributed to preexisting diabetes type 1 or 2. Preconception counseling of women with diabetes in the reproductive age group should include the employment of effective contraceptive methods until the woman is ready to become pregnant. Tight control if safely possible with a goal HbA1c of <6.5% should be attempted to reduce the risk of congenital anomalies, preeclampsia, macrosomia, and other complications [11].

DM Management During Pregnancy

In early pregnancy, there is increased glucose uptake by the placenta which is not insulin dependent; hence, fasting blood glucose readings are lower in women with normal glucose homeostasis. However, placental hormones are diabetogenic and this results is mild post prandial hyperglycemia. Many women with type 1 diabetes will have a decrease in their insulin requirements early in the pregnancy; which eventually reverses as the pregnancy progresses by about 16 weeks and insulin requirements may reach 2–3 times the pre-pregnancy requirements.

Fasting and postprandial blood sugars must be monitored during pregnancy in preexisting diabetes 1 or 2 in pregnancy and in gestational diabetes. Since HbA1c in pregnant women is slightly lower than in that of a non-pregnant women due to increase RBC turnover, the HbA1c goal is <6% if it can be achieved safely without hypoglycemia but may be relaxed to <7%. Fasting sugars should be <95 mg/dl and post-prandial sugars must be <140 mg/dl, or < 120 mg/dl for 1 h and 2 h respectively [12].

Most women who develop gestational diabetes can be managed by lifestyle modifications. If lifestyle measures are not sufficient, insulin is the first-line therapy. Metformin and glyburide may be used as second-line agents only as both cross the placenta to the fetus. In general, all oral medications lack long term safety data in pregnancy. Women who develop gestational diabetes should be tested at 4–12 weeks post-partum for the development of type 2 diabetes with an oral glucose tolerance test.

In the case of preexisting diabetes 1 or 2, insulin is again, the first-line therapy. Insulin requirements fluctuate during pregnancy but during the third trimester there is an increase in post prandial insulin requirements >50% when

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compared to basal insulin requirements. In the immediate postpartum state, insulin requirements decrease by about 50% and caution must be implemented to avoid hypoglycemia. Regular insulin, Aspart, Lispro, NPH, and Detemir are all pregnancy category B and may be safely used in pregnancy.

During pregnancy, women should be counseled about the risk of the development/progression of diabetic retinopathy. Close monitoring with a dilated eye exam should take place prior to pregnancy and every trimester if needed.

Diabetes during pregnancy often requires a multidisciplinary approach involving an endocrinologist, maternal-fetal medicine specialist, registered dietitian nutritionist, and diabetes educator, when available.

Dietary Considerations

All patients with type 1 or type 2 diabetes must be referred to medical nutrition therapy (MNT). Nutrition education should emphasize the consumption of nonstarchy vegetables, minimizing added sugars and refined grains, and choosing whole foods over processed foods to the extent possible. In addition, reducing overall carbohydrate intake for individuals with diabetes has shown evidence for improving glycemia. MNT visits should occur frequently, about 3–6 visits in the first 6 months after diagnosis and annually after that. People with prediabetes and obesity should be referred to intensive lifestyle intervention programs for weight loss. A weight loss of 7–10% is needed to prevent the progression to type 2 diabetes [13].

Exercise Considerations

Moderate exercise is recommended for about 30 min per day most days of the week for all patients with diabetes and is a cornerstone of intensive lifestyle modifications. Patients on insulin therapy must check blood sugar prior to onset of physical activity and snack if needed to avoid the development of hypoglycemia.

Other Routine Care for Patients with Type 1 Diabetes

Hypertension Management: Patients with hypertension and diabetes should monitor their blood pressure at home and their blood pressure should be measured at every clinic visit. For patients with type 1 diabetes who have a high cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely achieved. If the cardiovascular risk is <15% a blood pressure goal of <140/90 is acceptable [14].

Dyslipidemia: Lipid profile should be measured at diagnosis of diabetes and every 5 years if younger than age of 40 and more frequently above the age of 40. Patients with type 1 or 2 diabetes of all ages who have an atherosclerotic cardiovascular disease risk of more than 20%, should be started on high intensity statin. Any patient between 40 and 75 years of age with diabetes should be at least on a moderate intensity statin.

Diabetic Retinopathy: Patients with type 1 diabetes should start getting comprehensive eye exams 5 years after diabetes diagnosis.

Diabetic Nephropathy: Microalbuminuria screening should also be initiated 5 years after the diagnosis of type 1 diabetes.

Diabetic Neuropathy: Screening with monofilament testing should be initiated 5 years after type 1 diagnosis.

Vaccines: All adults with diabetes must receive the Tdap, pneumococcal vaccine, zoster vaccine, hepB vaccine, and influenza.

Foot Care: All patients with diabetes should be instructed to inspect feet regularly and seek podiatry care if needed.

Smoking Cessation: Smoking cessation must be addressed at least annually in all patients with diabetes.

Transplantation Consideration: Patients with type 1 diabetes who have received kidney transplantation or who are candidates for one, are also considered candidates for pancreatic

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transplantation in centers dedicated to performing these procedures.

Management of Type 2 Diabetes Mellitus

Type 2 DM was previously called noninsulin-dependent or adult onset diabetes. Patients with this disease account for over 90% of all patients diagnosed with diabetes. Classically, the disease initially begins as an insulin resistance state with higher levels of insulin secretion and at times a post-prandial reactive hypoglycemia. Over time, however, relative insulin deficiency leads to hyperglycemia. Patients with type 2 DM are often obese, have prior evidence for glucose intolerance. Women often have a prior history of gestational diabetes. Patients at higher risk for this disease include those who are African Americans, Hispanic/Latinos, Native American, and some who are Asian American. Although the disease is traditionally seen in older adults, it is being more recognized in children and adolescents as well as young men and women. Although infrequent, patients with type 2 DM can present with diabetic keto acidosis (DKA). Type 2 DM is a progressive disease that is initially characterized by being primarily an insulin-resistant state whereby glucose levels are normal while insulin levels are increased to maintain euglycemia. Over time, however, evidence for β cell function gradual failure emerges while the state of insulin resistance persists. The latter combination results in elevation in glucose levels initially post-prandial and subsequently in the fasting state. At the time of presentations for medical care, most patients with type 2 DM have already have evidence for microvascular complications of diabetes. As discussed earlier, a unique form of diabetes is what is described as maturity onset diabetes of the young (MODY). This is an autosomal dominant disease associated with β cell dysfunction leading initially to mild hyperglycemia often reaching the diagnostic criteria for diabetes and is usually diagnosed during adolescence or early adulthood.

Clinical Features in Patients with Type 2 Diabetes Mellitus

Risk factors for type 2 diabetes include the following: Age $\geq$ 45, Positive family history in a first degree relative, hypertension, dyslipidemia, sedentary lifestyle, history of gestational diabetes, overweight (BMI $\geq$ 25 kg/m^2), high risk ethnic group, prediabetes, polycystic ovarian syndrome.

Physical Exam findings include skin dryness, acanthosis nigericans (Fig. 2), central fat distribution, retinal hemorrhage or exudates, muscle atrophy, decreased sensation, loss of proprioception, foot ulcers.

In young patients who do not fit the typical findings, MODY should be considered, while in older patients who also do not fit these typical findings, LADA should be considered.

There are several pathophysiologic mechanisms that contribute to the development of hyperglycemia in patients with type 2 DM. These include at least the following mechanism;

1. Insulin resistance.
2. Impaired insulin secretion.
3. Decreased incretin effect.



Fig. 2 Acanthosis nigricans, which is dark discoloration and velvety texture of the skin present at skin folds such as neck and underarms

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4. Increased hepatic glucose production, decreased skeletal uptake, and questionable increase in its renal reabsorption.

Management of patients with type 2 DM involves a comprehensive approach that is aimed at addressing the basic pathophysiologic mechanisms for the disease itself as well as its known sequalae, such as the microvascular and macrovascular complications. While controlling glycemia is extremely important, it is by no means sufficient. Thus the management should address other aspects of the patients such as ensuring normal blood pressure, lipid levels, smoking cessation as well proper dietary intake and adequate appropriate exercise activity.

Pharmacologic Therapy of Type 2 Diabetes Mellitus

There are several classes of drugs used in the pharmacologic therapy of patients with type 2 DM. These drugs represent attempts to address specific pathophysiologic mechanisms involved in patients with type 2 DM. These are listed below:

1. Insulin sensitizers such as thiozolidinediones and metformin.
2. Insulin secretagouges such as sulfonylureas and glinides.
3. GLP-1 receptor agonists and DPP-4 inhibitors that decrease appetite and decrease GI motility, decrease glucagon and stimulate insulin secretion.
4. SGLT-2 inhibitors which increases glucosuria.
5. Insulin therapy.
6. Alpha glucosidase inhibitors which decrease glucose absorption.

There are important major concepts which should guide the pharmacologic management of type 2 diabetes. These include the following:

1. Metformin should always be a first-line therapy and should be continued unless its use becomes contraindicated.
2. Other agents can be added to metformin, including insulin.
3. Stepwise addition of medications should be performed until HbA1c is at goal.
4. Avoid combining medications which have a similar mechanism of action (such as DPP-IV inhibitors and GLP-1 RA).
5. It is recommended to start insulin therapy in the presence of symptomatic hyperglycemia BG $>$ 300 mg/dl, if HbA1c is $>$10%, or there is ongoing catabolism and weight loss.
6. In the presence of risk factors such as heart disease, kidney disease, or heart failure, an SGLT2 inhibitor or a GLP1-RA with demonstrated cardiac or renal benefit are recommended for use regardless of HbA1c.
7. Careful considerations need to be made for patients with ESRD (end stage renal disease) or liver cirrhosis since very few of these drugs have been studied for safety. Insulin (with particular attention to pharmacokinetics) is likely to be the safest option in these high risk patients.
8. Careful consideration should be made to cost, side effect profile of medications, hypoglycemia risk, impact on weight, and patient preference.
9. Reassessment of therapy should be made every 3–6 months until HbA1c is at goal.

Specific Pharmacologic Therapy for Type 2 DM

- **Metformin**: This medication is considered first-line therapy in patients with type 2 diabetes. It works by decreasing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake. It has a favorable metabolic profile, promotes modest weight loss, and can lower the HbA1c by about 1.5%. It is safe, effective and inexpensive and may reduce risk of cardiovascular events and death [7]. Importantly, it does not typically cause hypoglycemia. It is renally cleared and in the event of renal failure, it can be associated with lactic acidosis which is a rare occurrence. Hence, the FDA revised the label for use in patients with moderate kidney

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dysfunction as long as eGFR is >45 ml/min/1.73 m^2 and advised use with caution in patients with eGFR of 30–45 ml/min/1.73 m^2. Metformin is contraindicated in the setting of acute decompensated heart failure and liver cirrhosis. Principle side effects of metformin include bloating, abdominal discomfort and diarrhea that can be mitigated by gradual dose up titration. Extended release preparations have less gastrointestinal side effects. Metformin should be held prior to IV contrast administration given risk of kidney injury. In addition, long term use (>5 years) has been associated with vitamin B 12 deficiency, hence the need for periodic monitoring of vitamin B12 levels.

- **Thiazolidinediones**: The Thiazolidinediones increase insulin sensitivity by acting on adipose tissue and muscle to increase glucose utilization. To a lesser degree, they decrease glucose production by the liver. These agents are used as second line, or even more commonly, third-line therapy. The main side effects include fluid retention and peripheral edema and therefore they are contraindicated for use in patients with a history of congestive heart failure. They are also contraindicated for use in patients with active liver disease. There is also substantial evidence that they decrease bone density and increase the risk of fractures especially in women; therefore their use should be avoided in older individuals with risk for fractures. Additionally, there have been conflicting reports about use of pioglitazone and an increased risk of bladder cancer; therefore, they should be avoided in patients with a history of active bladder cancer. The main 2 medications in this class are pioglitazone and rosiglitazone. Rosiglitazone is no longer widely available and much more rarely used given some controversial concern for a potential increased risk of cardiovascular events. Pioglitazone may still offer an advantage in certain clinical settings; for example, in the context of high risk for hypoglycemia, severe insulin resistance, coexisting nonalcoholic steatohepatitis (NASH), or recent stroke. In fact, clinical trials have demonstrated a particular benefit in insulin resistant patients with a history of stroke and another benefit in improving fibrosis and inflammation in patients with non-alcoholic steatohepatitis (NASH) [15].
- **Sulfonylureas**: This class of medications falls under the secretagogue class, which act by stimulating insulin release from the pancreas. They have been available since the 1950s. They are highly effective in lowering blood glucose and can lower HbA1c by up to 1–2%. They are typically dosed once or twice a day. They have a neutral cardiovascular profile; however, their main side effect is that they can precipitate hypoglycemia and their use is cautioned especially in the elderly population. Another side effect is weight gain which results from increased endogenous insulin production. Glyburide is falling out of favor given increased risk of hypoglycemia; however, glipizide and glimepiride continue to be used especially given their low cost. They should be used in caution in patients with kidney disease given the augmented hypoglycemia effect. With the development of newer glucose lowering therapies that have a safer side effect profile, these medications are starting to fall out of favor overall.
- **Glinides**: This is another class of secretagogues which has a shorter half-life than sulfonylureas. It provides a faster and briefer stimulus to insulin secretion in comparison to sulfonylureas. It is typically taken with each meal and provides better postprandial control and has very little effect on fasting sugar control. The main available medications are repaglinide and nateglinide. Their main disadvantages are the need for multiple daily doses and their comparably higher cost.
- **DPP-IV inhibitors**: This class of medications are considered incretin-related therapies along with GLP-1 receptor agonists. These drugs inhibit the DPP-IV enzyme which is involved in the degradation of glucagon-like peptide-1 which results in a twofold increase in GLP-1 and GIP levels. This subsequently results in a reduction of pancreatic hypersecretion of glucagon and augmentation of glucose-dependent

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insulin secretion. These drugs are generally well tolerated with low risk of hypoglycemia and are dosed once daily. HbA1c reduction is intermediate up to 0.7% [7]. They are weight neutral and are not commonly associated with GI side effects. They have a potential risk of causing acute pancreatitis and are contraindicated in the setting of a known history of pancreatitis. They also can potentially cause joint pains. Examples of these medications include linagliptin, sitgaliptin, alogliptin, and saxagliptin. All are renally cleared except linagliptin, therefore require renal adjustment according to GFR.

- **GLP-1 receptor agonists (GLP-RA)**: This is another form of incretin based therapy. Due to their effectiveness, these medications should be attempted in the obese type 2 diabetic patients especially those who are overweight prior to the initiation of insulin. Often, they are used as second line agents in addition to metformin. The main difference when compared to DPP-IV inhibitors is that they achieve pharmacologic levels of levels of GLP-1 as compared to near the physiologic concentrations of GLP-1 when DPP-IV inhibitors are used. Figure 3 shows the physiologic mechanisms of incretin-based therapies. GLP-RA are known to delay gastric motility. This class of medications are highly efficacious drugs in terms of HbA1c lowering (1%). They do not result in hypoglycemia and have a significant weight loss benefit. Importantly, large randomized controlled trials have demonstrated an added benefit in terms of cardiovascular risk reduction in patients with known cardiovascular disease, with most of these medications (liraglutide, semaglutide, and dulaglutide) [16–18]; which makes them indicated for use in that setting. In addition, these drugs have also been found to potentially be beneficial in patients with CKD primarily by improving microalbuminuria [19]. These medications are safely used as long as the GFR > 30 ml/min/1.73 m^2. There has been some suggestion in the literature that liragulatide is safe in the setting of a GFR of $15 - 30$ ml/min/1.73 m^2, however, in general, they are not well studied in patients with ESRD and therefore use is not recommended. Commonly, these drugs are also very effective when added to basal insulin therapy to help with postprandial blood glucose spikes and to offset the weight gain resulting from the anabolic effect of insulin. Most formulations are administered via subcutaneous injection on a daily, twice daily, or weekly basis which creates a limitation for their use in patients with fear of injections. However, the once weekly formulation of these drugs (semaglutide, dulaglutide, exenatide) can perhaps offset this concern. The main side effects include nausea and vomiting; hence the recommendation for slow uptitration of dose such as

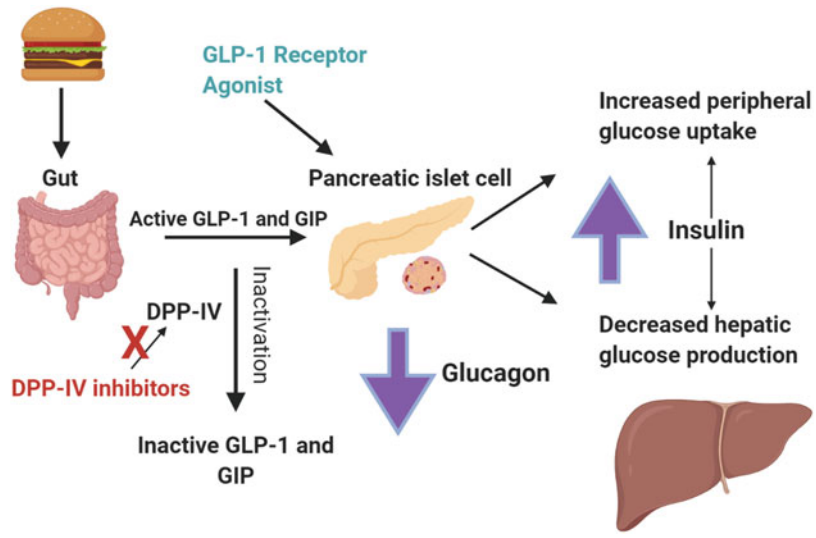


Fig. 3 Physiologic mechanisms behind incretin-based therapies

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with liraglutide. More recently, an oral GLP-1RA formulation (semaglutide) has been FDA approved for use in type 2 diabetes. It is important to note that these drugs have an FDA black box warning for risk of thyroid C-cell tumors and are contraindicated in the setting of history of medullary thyroid carcinoma. In addition, they do carry a risk of acute pancreatitis. The cost of these medications though is known to be very high.

- **SGLT2 inhibitors**: Sodium glucose cotransporter type 2 is expressed in the proximal renal tubule and mediates reabsorption of approximately 90% of the filtered glucose load. SGLT2 inhibitors promote the renal excretion of glucose by promoting osmotic diuresis. The ability to lower blood glucose is limited by the filtered load of glucose and the osmotic diuresis that is caused by this therapy. Therefore, their efficacy in lowering HbA1c is limited. They are dosed once per day and their risk for precipitating hypoglycemia is extremely low. Due to osmotic diuresis, they can result in blood pressure lowering and potentially AKI due fluid losses. However, they have emerged as a promising therapy for patients with type 2 diabetes with coexisting cardiovascular or renal disease for reduction of CV events, decreased hospitalizations for heart failure, and delaying the progression of kidney disease based on multiple large randomized controlled trials [20–22]. The mechanism of that benefit is quite yet to be fully elucidated, but is thought to be related to their diuretic effect, reduction in hyperfiltration at the kidney level, and potentially being a source of cardiac fuel. The main side effects include risk of acute kidney injury (typically transient) requiring monitoring of kidney function. It is certainly prudent to take into consideration co-therapy with other diuretic therapies and adjustment of doses as needed to avoid volume depletion. Importantly, there is an increased risk of urinary tract infections and genital mycotic infections in females and in males. The FDA has received reports of fatal urosepsis and incidence of Fournier's gangrene. The cost of these medications is considerably high.

Other noninsulin therapies used for the treatment of type 2 diabetes include pramlintide and alpha glucosidase inhibitors which are not very commonly used. Pramlintide is an analogue of amylin that is cosecreted by the pancreatic beta cells in response to food intake. It delays gastric emptying and suppresses glucagon secretion and reduces food intake by centrally suppressing the appetite. It has been studied in both patients with type 1 and type 2 diabetes. However, it requires injections with each meal in the setting of type 1 diabetes and at least twice daily in type 2 diabetes. It cannot be mixed in a syringe with insulin. Pramlintide therapy requires careful patient education and monitoring to avoid severe hypoglycemia. Due to these reasons it has fallen out of favor. Acarbose, which is an alpha glucosidase inhibitor, interferes with digestion and absorption of dietary carbohydrate and mainly influences postprandial blood glucose readings. Their frequent dosing with meals and their significant side effect profile such as nausea, flatus, and diarrhea have significantly limited their use in the diabetic population [7].

Insulin in Type 2 Diabetes: As mentioned prior, it is acceptable to initiate insulin at any time in the course of the disease, particularly if the HbA1c is significantly elevated >10%, if patients are symptomatic, or if there are contraindications for use of oral or injectable therapies. Careful consideration for insulin pharmacokinetics must be observed.

Patients who fail to achieve goal HbA1c on maximal therapy with oral and injectable agents should be started on insulin. Medications with proven cardiovascular benefits such as GLP-RA and SGLT2 inhibitors and pioglitazone must be continued along with insulin regardless of HbA1c, unless use is contraindicated.

Once the need for insulin therapy is ascertained, basal insulin must be started first at a dose of 10 units per day or 0.1–0.2 IU/kg. The next step would be setting a fasting glucose target which is 80–130 mg/dl [23]. Patients can be given instructions to up titrate the dose; for example, increase dose by 2 units every 3 days until fasting goal is achieved without hypoglycemia. For any unexplained hypoglycemia, insulin dose must be reduced by 10–20%. If using NPH as basal insulin, the dose can be split with ⅔ of the dose to be given during the day and ⅓ to be given at bedtime.

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Glargine insulin is usually administered at bedtime to provide fasting blood glucose control but can also be administered in the morning especially if patients tend to forget administering nighttime basal insulin. Degludec insulin can be administered any time of the day due to its peakless action. Long acting basal analogues such as U100 glargine and detemir have been demonstrated to reduce the risk of symptomatic and nocturnal hypoglycemia compared with NPH insulin; although these advantages are modest. U300 glargine (300 units/ml) or degludec may convey a lower hypoglycemia risk when compared with U100 glargine when used in combination with oral agents. If the HbA1c continues to be above target despite achieving target fasting glucose or once the basal dose is >0.5 IU/kg, then prandial insulin is the reasonable next step. However, if the patient is not on GLP-1 RA at this time, one can be added to basal insulin prior to adding prandial insulin. This combination can be very potent and provides less weight gain and hypoglycemia when compared with intensified insulin regimens. When adding prandial insulin, it should first be started with the largest meal. It can be started at 4 units per day or 10% of basal dose and this dose can be increased by 1–2 units every 3 days. Consideration should be given to decreasing the basal insulin dose especially after adding prandial insulin with the evening meal. If the HbA1c continues to be above target then more injections can be added gradually up to 3 injections per day with meals, which is a full basal-bolus regimen i.e. basal insulin and prandial insulin before each meal. Prandial insulin may be administered immediately after a meal in the event a patient has unpredictable oral intake. One can also consider twice daily premixed insulin regimen (NPH/regular or NPH/aspart) starting off from the same total daily dose, especially in patients with compliance issues provided they have fixed meal routines. A basal-bolus regimen offers greater flexibility for patients who eat on an irregular basis. Once a full basal and prandial insulin has been started it would be logical to stop medications such as secretagogues but continue medications such as metformin or medications with proven cardiovascular or renal benefits (Table 4).

Table 4 Oral agents for the treatment of type 2 diabetes

Class	Medication	Dosage strength	Dosing frequency	Maximum dosage
Biguanides	Metformin	500, 850, 1000 mg (also available in extended release form)	QD or BID AC	2000 mg
Sulfonylureas (second generation)	Glimepiride Glipizide Glyburide	1 mg, 2 mg, 4 mg 5 mg, 10 mg 2.5 mg, 5 mg	QD or BID before meals	8 mg 40 mg (IR), 20 mg(XL)
Thiazolidinediones	Pioglitazone	30 mg, 45 mg	QD	45 mg
Meglitinides	Nateglinide Repaglinide	60 mg, 120 mg 0.5 mg, 1 mg, 2 mg	TID before meals	360 mg 16 mg
DPP-IV inhibitors	Alogliptin Saxagliptin Sitagliptin Linagliptin	25 mg 2.5, 5 mg 25, 50 mg, 100 mg 5 mg	QD QD QD QD	25 mg 5 mg 100 mg 5 mg
GLP1-RA	Exenatide Dulaglutide Semaglutide Liraglutide	2 mg 0.75 mg, 1.5 mg 0.5 mg, 1 mg 1.8 mg	Weekly Weekly Weekly QD	2 mg 1.5 mg 1 mg 1.8 mg
SGLT2 inhibitors	Ertugliflozin Dapagliflozin Canagliflozin Empagliflozin	5 mg, 15 mg 5 mg, 10 mg 100 mg, 300 mg 10 mg, 25 mg	QD QD QD QD	15 mg 10 mg 300 mg 25 mg
A-glucosidase inhibitors	Acarbose Miglitol	25 mg, 50 mg, 100 mg 25 mg, 50 mg, 100 mg	TID AC TID AC	300 mg 300 mg
Amylin mimetic	Pramlintide	120 ug pen	Weekly	120 ug
Bile acid sequestrant	Colesevelam	625 mg	QD or BID	3.75 g

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Of note, the cost of insulin has been steadily rising over the last few decades at a high pace which poses a significant burden for patients and contributes to medication non-adherence. Consideration of cost is an important component of effective management. In these situations, human insulin (NPH and Regular insulin) may be the appropriate choice of therapy since they can be purchased at considerably lower prices.

Concentrated Insulin: U-500 regular insulin is 5 times more concentrated than U100. It has delayed onset and longer duration of action and acts more like NPH; it can be given as 2 or 3 injections per day. U-300 glargine and U-200 degludec and more recently U-200 lispro allow more units to be administered per volume. These are, for the most part, present in pen forms to decrease the chance of dosing errors.

Inhaled Insulin: This formulation of insulin is not commonly used. It is available in a limited dosing range for prandial use. Larger studies on inhaled insulin are needed. It is contraindicated for use in patients with chronic lung disease or patients who smoke.

Bariatric Surgery: Weight loss results in dramatic improvement in glycemic control and in some cases reversal of diabetes type 2. It may be indicated in the patient with type 2 diabetes who has a BMI >30 if glycemic control is poor. Above a BMI of 40, it is recommended regardless of control. The best results are seen with Roux-en-Y gastric bypass; however, it has the most side effects such as dumping syndrome, hypoglycemia, and vitamin deficiencies.

Glycemic Targets

The main test for assessing glycemic management is the HbA1c, it should be used in addition to self-monitoring of blood glucose (SMBG). HbA1c should be checked every 6 months in patients with adequate control and quarterly in patients not meeting glycemic targets. Point of care HbA1c testing is helpful in making timely adjustments. An HbA1c goal for many non-pregnant adults of <7% is appropriate. Achieving an HbA1c of <6.5% in the appropriate patient population (young, healthy, without comorbidities) is appropriate if it can be achieved safely. In pregnant patients, tight control <6.5% is required to decrease maternal and fetal morbidity. Less stringent goals <8%, might also be appropriate in patients with severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin [24]. Fig. 4 depicts a framework for individualizing glucose targets based on multiple factors.

Step-Wise Introduction of Therapeutic Agents

While it is clear that metformin should be the first drug to be used in the initial management of type 2 diabetes, the sequence of additional drugs when metformin fails can vary from one patient to another. A summary of potential sequential use of drugs is illustrated in Fig. 5.

Other Routine Medical Care in Type 2 Diabetes Patients

Eye Exam: All patients must obtain a dilated eye exam at diabetes diagnosis and at least yearly depending on initial findings.

Smoking: All patients with diabetes must be counseled about smoking cessation to decrease the risk of atherosclerotic CVD.

Hypertension: Goal BP must be individualized based on comorbidities. ACE inhibitors are first line especially if there is microalbuminuria.

Dyslipidemia: All diabetic patients above the age of 40–75 must be on a moderate to high intensity statin.

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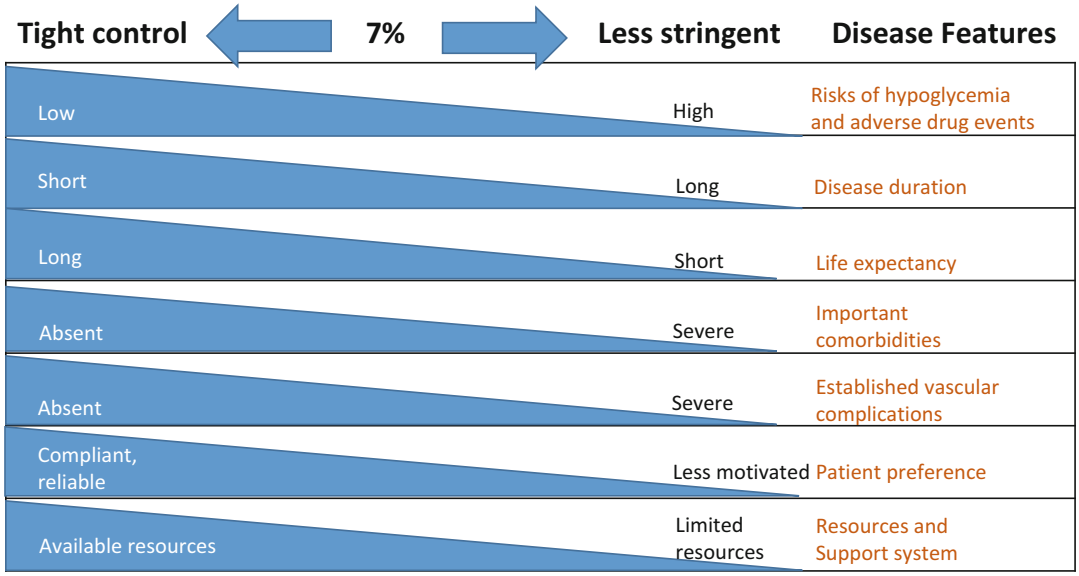


Fig. 4 Individualization of blood glucose targets

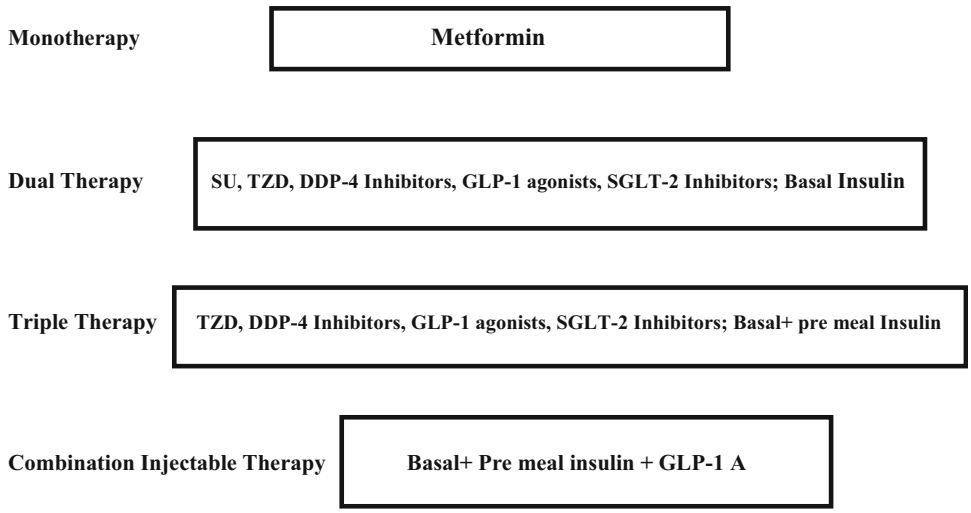


Fig. 5 Management of hyperglycemia in type 2 DM

Alcohol: Patients must be cautioned about risk of hypoglycemia with alcohol use especially if they are on insulin therapy.

Foot Care: Patients should be instructed to inspect and wash but not soak feet, daily; keep nails trimmed, and seek podiatric care if needed.

Vaccines: All adults with diabetes must receive the Tdap, pneumococcal vaccine, zoster vaccine, hepB vaccine, and influenza.

Complications of Diabetes Mellitus

Microvascular Complications

1-Diabetic Retinopathy: Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. It is a highly specific vascular

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complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic control. Factors that increase the risk of retinopathy include chronic hyperglycemia, nephropathy, hypertension, and dyslipidemia. Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy. Blood pressure and lipid control are also important in slowing the progression [25]. Pregnancy is associated with a rapid progression of diabetic retinopathy. Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy.

Diabetic Nephropathy: Diabetic kidney disease occurs in 20–40% of patients with diabetes. CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation. The diagnosis is made based on the presence of albuminuria and/or reduced eGFR. Therefore, it is recommended to assess urinary albumin (e.g., spot urinary albumin to creatinine ratio) and eGFR in patients with type 1 diabetes with duration of 5 or more years, in all patients with type 2 diabetes and in all patients with comorbid hypertension. Optimizing glucose control is crucial to reduce the risk or slow the progression of chronic kidney disease [25]. The ADA has added new guidelines involving the use of SGLT2 inhibitors and GLP-1-Receptor Agonists. For patients with type 2 diabetes and chronic kidney disease, the use of an SGLT 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both; should be considered unless the risk outweighs the benefit [14]. BP control is also of paramount importance. In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an ARB is recommended for use in those with modestly elevated urinary albumin–creatinine ratio (30–299 mg/g creatinine) and strongly recommended with a ratio of more than 300 mg/g creatinine and/or eGFR <60 ml/min/1.73 m^2. For patients with CKD, dietary protein intake should be approximately 0.8 g/kg body weight per day. Periodic monitoring of serum creatinine and potassium must be performed. Patients should be referred for consideration of renal replacement therapy if GFR <30 ml/min/1.73 m^2, or if there is concern about another etiology for kidney disease, or for rapidly progressing disease [25].

Diabetic Neuropathy

Patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes should be assessed annually for the development of diabetic neuropathy. Patients should have an annual foot exam including a 10-g monofilament testing to identify feet at risk for ulceration and amputation. Patients with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. Symptoms and signs of autonomic neuropathy should also be assessed in patients with microvascular complications. The treatment involves optimizing glucose control to prevent or delay the development of neuropathy in patients with type 1 diabetes and to slow the progression of neuropathy in patients with type 2 diabetes. The ADA recommends the use of duloxetine, pregabalin, and gabapentin as pharmacologic therapy for painful diabetic neuropathy. Both duloxetine and pregabalin are FDA approved for this indication. The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, or history of amputation [25].

Other Considerations

As mentioned previously, diabetes is considered an independent risk factor for the development of ASCVD (atherosclerotic cardiovascular disease). Coexisting conditions that are clear risk factors include hypertension, dyslipidemia, and smoking. Benefits are seen when multiple risk factors are addressed simultaneously. Heart failure is also another cause of morbidity and mortality from

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CVD. In addition, heart failure hospitalizations are two fold higher in patients with diabetes compared to patients without diabetes. Recent data has shown that SGLT2 inhibitors improve the rates of heart failure hospitalizations in patients with type 2 diabetes [21]. Treatment for HTN should include drug classes to reduce cardiovascular events such as ACE inhibitors and ARBs particularly if they have concomitant albuminuria.

As far as lipid management, patients with diabetes aged 40–75 should be initiated on a moderate intensity statin in addition to lifestyle therapy. High-intensity statin should be initiated for patients with diabetes and concomitant ASCVD. PCSK9 inhibitors should be used in patients with ASCVD and diabetes whose LDL is>70 mg/dl on maximal statin and LDL lowering therapy. In addition, recent studies have shown that in patients with ASCVD or other cardiovascular risk factors on a statin with a controlled LDL but elevated Triglyceride levels 135–499, the addition of icosapent ethyl can be considered to reduce vascular risk [26]. Aspirin therapy is effective in secondary prevention in patients with diabetes and ASCVD. However, it may be considered in patients with diabetes as primary prevention after weighing the risks (mainly GI bleeding) versus the benefits.

Diabetic Emergencies

Diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic state (HHS) are the two most serious acute metabolic complications of diabetes.

Most patients with DKA have type 1 diabetes and can develop this complication in the setting of a minor illness such as an upper respiratory tract infection and/or noncompliance with insulin intake. However, patients with type 2 diabetes are also at risk of developing DKA during the catabolic stress of acute illness such as trauma, surgery, or infections. DKA results in death 1–5% of patients. DKA is characterized by severe hyperglycemia, metabolic acidosis, and increased total body ketone concentration. The state of insulin deficiency results in free fatty acid oxidation and the formation of ketones, which results in ketonemia, high anion gap ketoacidosis, and ketonuria. Typically symptoms are acute and patients present within few days with polyuria and polydipsia, along with a constellation of malaise, abdominal pain, nausea, and vomiting. Patients are profoundly dehydrated and can present with hemodynamic instability. In severe cases, patients have altered mental status and obtundation which is life threatening if not managed promptly.

HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. HHS symptoms can develop over a period of days to weeks due to typically continued though insufficient insulin secretion. These metabolic derangements result from the combination of absolute or relative insulin deficiency and an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). Mortality attributed to HHS is considerably higher than that attributed to DKA, with recent mortality rates of 5–20% [27].

Diagnostic Testing for DKA and HHS

Typical physical exam findings include poor skin turgor, Kussmaul respirations (in DKA), tachycardia, and hypotension. Mental status can vary from full alertness to profound lethargy or coma, with the latter more frequent in HHS. Lab testing reveals hyperglycemia. In cases of DKA, blood glucose levels are >250 mg/dl and typically higher in HHS. Electrolyte abnormalities are also common and include hyponatremia and hyperkalemia. The admission serum sodium is usually low because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycemia. An increased or even normal serum sodium concentration in the presence of hyperglycemia indicates a rather profound degree of free water loss. To assess the severity of sodium and water deficit, serum sodium may be corrected by adding 1.6 meq/L to the measured serum sodium for each 100 mg/dl of glucose above 100 mg/dl.

Hyperkalemia often occurs because of an extracellular shift of potassium caused by insulin

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deficiency along with acidemia since insulin promotes the intracellular flux of potassium. Patients with low normal or low serum potassium concentration on admission have severe total-body potassium deficiency and require careful cardiac monitoring and more vigorous potassium replacement. Acute kidney injury is common and is caused by dehydration and usually reverses with fluid resuscitation.

The key diagnostic feature between DKA and HHS is elevated total blood ketone concentration. Accumulation of ketoacids results in an increased anion gap metabolic acidosis. The anion gap is calculated by subtracting the sum of chloride and bicarbonate concentration from the sodium concentration: [Na - (Cl + HCO3)]. A normal anion gap is between 7 and 9 mEq/l, and an anion gap 10–12 mEq/l indicates the presence of increased anion gap metabolic acidosis.

Management: DKA management involves aggressive fluid resuscitation and the co-administration of intravenous insulin, which serves to metabolize the ketones and alleviate the acidosis.

Fluid and Insulin Therapy: Initial fluid therapy is directed toward expansion of the intravascular, interstitial, and intracellular volume and restoration of renal perfusion; all of which are reduced in hyperglycemic crises. In the absence of cardiac compromise, isotonic saline (0.9% NaCl) is infused at a rate of 15–20 ml kg body weight in the first hour or 1–1.5 l during the first hour. Subsequent choice for fluid replacement depends on hemodynamics, the state of hydration, serum electrolyte levels, and urinary output. Fluid replacement should correct estimated deficits within the first 24 h.

The mainstay in the treatment of DKA involves the administration of regular insulin via continuous intravenous infusion or by frequent subcutaneous injections. The administration of continuous intravenous infusion of regular insulin is the preferred route because of its short half-life and easy titration as compared to the delayed onset of action and prolonged half-life of subcutaneous regular insulin. Typically an initial bolus of 0.1 u/kg is given followed by an infusion rate of 0.1 u/kg/h. Once blood glucose levels drop below 200 mg/dl, the infusion rate can be reduced by around 50% and 5% dextrose should be added to replacement fluids to allow continued insulin administration until ketonemia is controlled while at the same time avoiding hypoglycemia.

Despite total-body potassium depletion, mild-to-moderate hyperkalemia is common in patients with hyperglycemic crises. Insulin therapy, correction of acidosis, and volume expansion decrease serum potassium concentration. To prevent hypokalemia, potassium replacement is initiated after serum levels fall below the upper level of normal for the particular laboratory (5.0–5.2 mEq/l). Generally, 20–30 mEq potassium in each liter of infusion fluid is sufficient to maintain a serum potassium concentration within the normal range.

Patients with DKA and HHS should be treated with continuous intravenous insulin until the hyperglycemic crisis resolves. Criteria for resolution of ketoacidosis include a blood glucose less than 200 mg/dl and two of the following criteria: a serum bicarbonate level 15 mEq/l, a venous pH 7.3, and a calculated anion gap less than 12 mEq/l. When this occurs, subcutaneous insulin therapy can be started. To prevent recurrence of hyperglycemia or ketoacidosis during the transition period to subcutaneous insulin, it is important to allow an overlap of 1–2 h between discontinuation of intravenous insulin and the administration of subcutaneous insulin. In insulin-naïve patients, a multidose insulin regimen should be started at a dose of 0.5–0.8 units per kg per day.

Inpatient Diabetes Care

It is well known that inpatient hypoglycemia and hyperglycemia are associated with adverse outcomes. Hence, it is rather important to control hyperglycemia prior to admission for elective procedures, have inpatient protocols for management, and prepare an outpatient discharge plan for management and transition of care. Consulting with a diabetes management team should be done when possible. All patients admitted who have preexisting diabetes must get an HbA1c test if it has not been performed in the last 3 months. The use of validated computerized protocols that allow set adjustments in insulin dosage is recommended for use in the hospital to help with blood glucose fluctuations. In addition, a set

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hypoglycemia protocol must be ordered on all patients with diabetes regardless of insulin use. Factors such as the quantity of oral intake, route of nutrition (enteral vs. parenteral nutrition), NPO status, kidney function, and hypoglycemia risk must be taken into consideration. In patients with new onset hyperglycemia, treatment with insulin must start at a threshold of 180 mg/dl. A target glucose of 140–180 mg/dl is the goal for the majority of patients (noncritically ill and critically ill patients) based on a large randomized controlled trial which was done on critically ill patients, the NICE-SUGAR trial which showed no advantage of tightly controlled glycemia (110–140 mg/dl) but rather increased hypoglycemia rates and perhaps slightly increased mortality. A goal of 110–140 mg/dl may be appropriate for certain patients such as post-surgical patients and patients post cardiac surgery, if this can be achieved safely. Less stringent targets >180 mg/dl are acceptable in terminally ill patients or patients with severe comorbidities.

For patients who are noncritically ill with poor PO intake or NPO, the preferred regimen is basal insulin with bolus correction scale. For patients with good oral intake, basal, prandial plus correction scale regimen is the preferred treatment. In patients who are well controlled on their outpatient insulin regimen, a reduction of 25–50% of their home insulin requirements must be done on admission. Using a sliding scale alone during hospital stay is discouraged. Premixed insulin regimens are generally avoided in the inpatient setting. In some cases with type 2 diabetes, patients' oral home regimens may be continued if oral intake is adequate. A reduction in home oral sulfonylureas dosage is advised if those are continued. Metformin may be continued if no procedures are planned including those involving IV contrast and if kidney function allows the safe continuation of this medication. If oral medications are held on admission, it is recommended to restart them 1–2 days prior to discharge. Dipeptidyl peptidase 4 inhibitors may be initiated in specific groups of hospitalized patients to manage hyperglycemia; however, some (saxagliptin) should be avoided in patient with heart failure.

In the critically ill setting, intravenous insulin use is the most effective method for achieving glycemic targets when used according to set protocols.

In type 1 diabetes patients, caution must be taken to ensure basal insulin is administered regularly at all times. Patients on insulin pump therapy may in certain situations continue using their pumps if they are deemed proficient in counting their carbohydrates and managing their glycemic fluctuations through using their pumps. These patients should be advised to reduce their basal rates by at least 20% during hospital admissions or NPO status.

In patients on parenteral nutrition (TPN), ideally the insulin requirements can be calculated by using an IV insulin infusion and then converting 80% of that amount and adding that to the TPN solution over 24 h. In patients on enteral nutrition, long-acting insulin daily or intermediate acting twice daily may be used along with sliding scale. In patients on cycled tube feeds, for example, overnight, the ideal insulin might be NPH which has an activity that lasts a similar duration of time.

Inpatients on Glucocorticoids (GC): Patients on GC therapy develop GC-induced hyperglycemia. They commonly have high insulin requirements particularly in the prandial form. The effect of hyperglycemia when GC are administered is related to their duration of action but typically their effect will last throughout the day when given in the morning. Long acting GC such as dexamethasone have an effect which will last >24 h and long acting insulin along with prandial insulin is often required for adequate control. Caution must be taken when GC therapy is abruptly discontinued (such as with chemotherapy protocols), as continued insulin therapy may result in profound hypoglycemia.

Inpatient new insulin start: In patients who develop hyperglycemia in-house or who are diagnosed with diabetes in the hospital, basal insulin may be started at a 0.2–0.3 u/kg and prandial insulin at 0.05–0.1 u/kg/meal for patients who have adequate PO intake.

Inpatient glucose monitoring: Blood glucose monitoring must be performed every 4–6 h via finger stick in patients who are NPO or on continuous tube feeding or parenteral feeding and before

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meals and at bedtime for patients who are not NPO. There is currently insufficient data for recommending CGM use in hospitalized patients.

Finally, discharge planning should begin on admission. Patients who are admitted to the hospital and who develop new onset hyperglycemia or diabetes should be given diabetes education while admitted and the proper transition of care to the outpatient provider must be performed prior to discharge [28].

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Thyroid Disease

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Melanie Menning

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Overview

The thyroid is a 15–20 g gland located in the anterior neck whose role is to primarily make thyroxine (T4), as well as small amounts of triiodothyronine (T3). The majority of T3 is formed through extra-thyroidal conversion of T4. Thyroid hormone production is controlled through negative feedback regulation through the release of thyroid-stimulating hormones (TSH) by the pituitary gland which is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus [1].

Thyroid hormone is key in the regulation of protein, carbohydrate, and lipid metabolism, thermogenesis, and the development of the brain, intestine, bone, skeletal muscle, and auditory system [2, 3].

Thyroid Lab Testing

The most sensitive measure of thyroid hormone levels is TSH with subsequent confirmation with free T4 and T3. The TSH assay, however, can be affected by heterophilic antibodies and biotin intake. Samples in which heterophilic antibodies are suspected should be repeated in another assay or with serial dilutions. Biotin intake should be stopped at least 2 days prior to testing as to not interfere with the assay [3].

Hypothyroidism

A deficiency in circulating thyroid hormone results in hypothyroidism. Patients with overt hypothyroidism will have an elevated TSH with low or undetectable levels of T3 and T4. Patients with subclinical hypothyroidism have elevated TSH levels with normal levels of T3 and T4. Within the USA the prevalence of overt hypothyroidism is 0.3–0.4% with subclinical hypothyroidism prevalence between 4.3% and 8.5% [1, 4]. Worldwide, the most common cause of hypothyroidism is iodine insufficiency, with patients presenting with a large goiter. Iodine deficiency; however, is very rare in the USA [2, 4]. Other etiologies of hypothyroidism include Hashimoto's thyroiditis, iatrogenic from thyroidectomy or radioactive iodine treatment, congenital, infiltrative disease, and in rare cases decreased TSH production from the pituitary gland [1, 2]. Hypothyroidism is eight to nine times more common in women than men with an increased prevalence with age. It is more prevalent in white individuals than black or Hispanic [2, 4]. TSH naturally increases with age; however, these increases are usually asymptomatic and subclinical [2].

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Clinical Presentation

Patients with hypothyroidism have variable presentations with symptoms often not appearing until late in the disease process. Symptoms are often nonspecific and have a low sensitivity and positive predictive value for hypothyroidism. Patients may note fatigue, lethargy, poor concentration, impaired memory, weight gain, tinnitus, vertigo, polyneuropathy, tremor, obstructive sleep apnea, depressed or anxious mood, menstrual irregularities, impotence, decreased libido, constipation, cool and dry skin, hair loss, non-pitting edema (myxedema), enlarged tongue, husky, low-pitched voice with slowed speech, brittle and thickened nails, muscle cramps, and proximal muscle weakness [2, 4]. Hypothyroidism has been associated with decreased quality of life, increased sick leave, and increased mortality [4]. Prolonged hypothyroidism can result in severe complications including atrial fibrillation, coronary artery disease, and increased fracture risk due to osteoporosis. If hypothyroidism occurs during the fetal and neonatal stages, more profound effects can be seen including severe intellectual deficits, impaired fine motor skills, spasticity, impaired balance, and deafness [2].

Diagnostic Evaluation

Workup for hypothyroidism begins with TSH, T4 and T3 levels. Elevated TSH with depressed T4 and T3 levels is consistent with primary hypothyroidism or hypothyroidism originating from the thyroid gland itself. Low or inappropriately normal levels of TSH with depressed T4 and T3 levels are consistent with central hypothyroidism or hypothyroidism originating from the pituitary or hypothalamus gland with an otherwise normal thyroid gland [2].

Hypothyroidism is also associated with other lab abnormalities. Hypothyroidism has been associated with increased insulin resistance, but decreased insulin degradation resulting in a higher risk of hypoglycemia in diabetics. It additionally affects lipid metabolism resulting in increased low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Liver enzymes and creatinine kinase may also be elevated. Patients may have a depressed GFR and hyponatremia. Anemia may be present in up to 30% of adults and 60% of kids. EKG and echocardiogram may reveal evidence of cardiomegaly, depressed diastolic and systolic function, and prolonged QTC [2].

Treatment

The mainstay treatment for hypothyroidism is thyroid hormone replacement with levothyroxine (LT4), which is identical to T4. A synthetic version of thyroid hormone first became available in the 1950s and is now the mostly commonly prescribed medication in the USA. Levothyroxine is initiated using weight-based dosing of 1.6 μg/kg/day with females requiring 75–125 μg daily and males requiring 100–150 μg daily [2, 4]. Lower doses should be utilized in the elderly and individuals with coronary artery disease, often starting at a dose of 25–50 μg [4]. It take 6–8 weeks to reach a steady state, and TSH should be checked at that time. Most guidelines recommend against the addition of L-triiodothyronine (LT3) to levothyroxine as it has not consistently proven beneficial in trials [2, 4]. Furthermore, desiccated thyroid supplementation is not recommended due to large variations in levels of thyroid hormones between batches [2].

Thyroid hormone is primarily absorbed in the small intestine and has higher absorption levels if taken fasting and separate from other medications. Other comorbid conditions and medications that affect gastric acid secretion or small bowel absorption, such as celiac disease or prior bowel surgery, result in decreased absorption of levothyroxine and need for increased dosing. The liquid formulation is better absorbed than the tablet formulation. Many medications also affect levothyroxine absorption (Table 1) [2]. Levothyroxine has a half-life of 1 week. This allows for thyroid hormone to be given in daily or weekly dosing. Levothyroxine should be taken 30 min prior to the first meal of the day and separate from other medications [2, 4].

Additionally, certain medical conditions can affect thyroid hormone levels including

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Table 1 Medication effects on thyroid hormone levels [2]

Medication	Effect
Bile acid sequestrants	Decreases absorption. Take 4–5 h apart
Sucralfate	Decreases absorption
Ferrous sulfate	Decreases absorption
Calcium carbonate	Decreases bioavailability
Phosphate binders	Decrease bioavailability
Raloxifene, orlistat	Decrease absorption
Estrogen	Increase thyroid-binding globulin decreasing clearance
Selective estrogen receptor modifiers	Decreases clearance
Antiepileptics	Decrease absorption, increase clearance
Tuberculosis medications	Decrease absorption, increase clearance
Tyrosine kinase inhibitors	Alter thyroid regulation

pregnancy, Addison's disease, and pernicious anemia. Pregnancy results in increased levels of thyroid-binding globulin resulting in decreased availability of thyroid hormone and the need to increase dosing by 25–50%. If a patient is experiencing severe morning sickness, dosing can be taken at night. In Addison's disease thyroid levels will often be low due to decreased glucocorticoids; however, glucocorticoid replacement alone often corrects the thyroid dysfunction. In fact, replacing thyroid hormone before correcting the glucocorticoid deficiency can precipitate adrenal crisis. Pernicious anemia also decreases thyroid hormone absorption and increases the dosing needed for replacement [2].

Myxedema Coma

Myxedema coma is a life-threatening systemic decompensation as a result of severe hypothyroidism. It is most common in elderly women. It can be triggered by cold temperatures, infections, medications, nonadherence to thyroid replacement and other serious comorbidities such as stroke and heart failure. Patients present with extreme lethargy and in severe cases coma. They are often hypothermic, bradycardic, hypercapnic, and hyponatremic and have renal impairment. Failing to recognize and treat myxedema coma in a timely fashion can result in death with a mortality rate of 25–60% despite appropriate treatment. Lab work will reveal severely low of undetectable levels of T4. TSH may be low or normal in patients with central hypothyroidism or elevated in patients with primary hypothyroidism. Patients suffering from myxedema coma should be cared for by a multidisciplinary team in the intensive care unit. Treatment consists of aggressive thyroid hormone replacement with a loading dose of 200–400 μg of levothyroxine given intravenously followed by a maintenance dose of 1.6 μg/kg/day orally. Patients also require supportive care including intravenous fluids, electrolytes, warming blankets, and stress-dose steroids [1].

Hashimoto's Thyroiditis

Hashimoto's thyroiditis was first described in 1912 and is the most common autoimmune disorder with a prevalence of 10–12% [2]. Hashimoto's thyroiditis results in a lymphocytic infiltration of the thyroid resulting in destruction, atrophy, and fibrosis [2, 5]. Hashimoto's thyroiditis is the most common cause of hypothyroidism in iodine-rich areas accounting for 20–30% of hypothyroid patients. Hashimoto's thyroiditis has an incidence rate of 0.3–1.5 per 1000 subjects per year [5]. It is found in females at a rate ten times higher than the rate in males [2, 5]. Its prevalence increases with age. It is most common in white individuals at a prevalence of 14.3% and least common in African Americans with a prevalence of 5.3% [2]. Hashimoto's thyroiditis is more common in individuals who have other autoimmune disorders and those with a family history of Hashimoto's with a 29–55% monozygotic twin concordance rate. Up to 50% of the siblings of patients with Hashimoto's thyroiditis will also have circulating antithyroid antibodies [5].

Diagnostic Workup

Physical exam may reveal a firm, enlarged thyroid or a non-palpable atrophic thyroid. Some

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patients may have a goiter. The diagnosis of Hashimoto's thyroiditis is made based on the presence of hypothyroidism (elevated TSH with low T4 and T3) and the presence of thyroid peroxidase (TPO) antibodies, which are present in 80–90% of patients and/or the presence of antithyroglobin antibodies, which are present in 60–80% of patients. Of note, patients with other thyroid dysfunction can also have these antibodies present. About 40–60% of patients with Graves' disease will have antithyroglobin antibodies present, and 50–60% will have TPO antibodies [2, 5]. Additionally, women with postpartum thyroiditis may have TPO antibodies present, and this is predictive of progression to permanent hypothyroidism. In patients with subclinical hypothyroidism, the presence of TPO antibodies predicts progression to overt hypothyroidism [5]. If thyroid ultrasound is obtained, it will reveal a hypoechogenic, dyshomogenous parenchyma [2, 5]. The hypoechogenic appearance on ultrasound may be present even before TPO antibody development [2]. Cytology and radioactive iodine uptake are not needed to make the diagnosis [5].

Treatment

Hashimoto's thyroiditis cannot be cured. Thyroid hormone replacement will however alleviate symptoms. Start levothyroxine at 1.5–1.7 μg/kg daily. Hashimoto's thyroiditis has been associated with papillary thyroid cancer. Due to this there should be a low threshold for thyroidectomy if there are any suspicious lesions [5].

Iatrogenic Hypothyroidism

Another common cause of hypothyroidism is iatrogenic. This includes hypothyroidism secondary to thyroidectomy, iodine ablation, external irradiation, antithyroid drugs, and other medications such as lithium, ethionamide, sulfonamides, iodine, tyrosine kinase inhibitors, and cytokines which can have destructive effects on the thyroid. These conditions are often permanent and require thyroid hormone replacement [2].

Painless Thyroiditis, Postpartum Thyroiditis, and Subacute Thyroiditis

Painless thyroiditis, postpartum thyroiditis, and subacute thyroiditis have a triphasic course which may include a hypothyroid period. The hypothyroid phase is often self-limited and only requires treatment if patients are symptomatic [2]. These conditions are discussed further in detail in the section on "Hyperthyroidism."

Riedel's Thyroiditis

Riedel's thyroiditis is a very rare chronic sclerosing replacement of the thyroid gland with connective tissue overgrowth into adjacent structures. This rare condition requires specialist assistance in diagnosis and treatment [6].

Thyroid Infiltration

Certain systemic conditions such as amyloidosis, hemochromatosis, sarcoidosis, cystinosis, and scleroderma can have local, destructive effects on the thyroid resulting in hypothyroidism [2]. These conditions are beyond the scope of this chapter, but further information can be found in other chapters on these conditions.

Congenital Hypothyroidism

Congenital hypothyroidism is the most frequent congenital endocrine disorder occurring in 1 out of every 3000–4000 of all live births. It is most commonly seen in Hispanic and Asian individuals. It occurs due to congenital TSH deficiency or TRH defect. Congenital hypothyroidism is now included on newborn screening, which allows for early identification and treatment to

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avoid the previous severe consequences of this disease [2].

Central Hypothyroidism

Central hypothyroidism is a rare cause of hypothyroidism with a prevalence of 1 in 20,000 to 1 in 80,000 individuals. Central hypothyroidism occurs due to pituitary or hypothalamic dysfunction resulting in insufficient TSH stimulation of a normal thyroid gland. Unlike other causes of hypothyroidism, central hypothyroidism has equal prevalence regardless of gender and age. It can occur for many reasons including pituitary invasion by benign or malignant tumors or aneurysms, iatrogenic dysfunction due to prior surgery, radiation or medications, injury, pituitary infarction, infiltrative disease such as hemochromatosis, sarcoidosis, or histiocytosis or infectious causes such as tuberculosis, syphilis, and mycoses. Identification of central hypothyroidism requires further evaluation of the other pituitary hormones and pituitary imaging with MRI. Central hypothyroidism is treated with hormone replacement often under the direction of endocrinology. Free T4 is monitored for treatment efficacy instead of TSH [2].

Hyperthyroidism

An excess in circulating thyroid hormone results in thyrotoxicosis. It is referred to as hyperthyroidism when it is the result of excess hormone synthesis or excretion. Thyrotoxicosis without hyperthyroidism occurs when preformed thyroid hormone is released from damaged follicles in the thyroid or through the introduction of thyroid hormone from extrathyroidal sources [7]. In the USA, the overall prevalence of hyperthyroidism is 1.2% with 0.5% of patients having overt hyperthyroidism (low TSH with elevated T3 and/or T4) and 0.7% having subclinical hyperthyroidism (low TSH with normal T3 and T4) [3]. The incidence of hyperthyroidism is higher in women than men. Rates of hyperthyroidism increase with age. It is most frequently found in the Caucasian individuals [7].

Clinical Presentation

Symptoms of thyrotoxicosis can vary by patient and do not strongly correlate with levels of free T4 and T3. Additionally, older patients often have fewer symptoms then their younger counterparts [3]. Symptoms may include weight loss, atrial fibrillation, tachycardia, anxiety, muscle weakness, fatigue, tremor, polydipsia, menstrual irregularities, infertility, sleep disturbance, heat intolerance, fatigue, diaphoresis, confusion, and edema [1–3, 7]. Long-standing thyrotoxicosis can result in osteoporosis, embolic events, cardiovascular collapse, and even death [3]. Thyrotoxicosis can also result in thyrotoxic periodic paralysis, a rare condition most common in the Asian population, which results in muscle paralysis, acute hypokalemia, and thyrotoxicosis [2, 7]. Older patients tend to have fewer symptoms but are at higher risk for major complications [7]. Individuals over the age of 60 have a three times increased risk of developing atrial fibrillation resulting in increased risk of embolic stroke as well [7].

Diagnostic Workup

Workup for thyrotoxicosis should not delay treatment especially in severe cases. Initial workup for thyrotoxicosis should include a comprehensive history and physical exam. A patient with thyrotoxicosis may be found to be tachycardic, hypertensive, and tachypneic. The thyroid may be diffusely enlarged or nodular and may be tender depending on the cause [3]. Additional possible signs include exophthalmos, tremor, hyperreflexia, and thyroid dermopathy, which are slightly thickened, discrete violaceous plaques on the shins and dorsum of feet, pretibial myxedema, and peripheral edema with or without acropachy [1, 3, 7]. Initial lab workup includes TSH, free T4, and total T3. In cases of overt hyperthyroidism, TSH will be undetectable with

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elevated T4 and/or T3 [7]. In subclinical hyperthyroidism, TSH is elevated but still detectable with normal levels of T4 and T3 [7] In elderly patients or patients with multiple comorbidities an EKG, Holter monitor and echocardiogram should be considered given high risk of cardiovascular complications [3].

Once a patient has been identified as being hyperthyroid, workup should include a thyroid radioiodine uptake scan and serum testing for antibodies including thyrotropin (TSH-R) receptor antibodies and thyroid-stimulating immunoglobulin (TSI) [7]. TSH-R and TSI will be present in Grave's disease but not in other conditions resulting in hyperthyroidism [3, 7]. Radioiodine uptake scan will reveal diffuse increased uptake in Graves' disease, localized increased uptake in toxic adenoma, and normal or decreased uptake in subacute thyroiditis, postpartum thyroiditis, painless thyroiditis, excess iodine intake, and factitious ingestion of thyroid hormone [3]. Thyroid ultrasound may help in treatment planning, for example, by identifying a nodule suspicious of malignancy, but offers little additional benefit in the workup of hyperthyroidism in comparison to antibody and radioactive iodine uptake testing [3, 7].

Thyroid Storm

In severe cases, thyrotoxicosis can result in a rare, but emergent condition known as thyroid storm. Thyroid storm is hyperthyroidism with severe life-threatening manifestations that is triggered by trauma, surgery, infection, inappropriate medication use, excessive iodine exposure, or severe health conditions [1, 7]. In 70% of cases, a trigger can be identified with the most common reason being nonadherence to antithyroid drugs followed by infection [7]. Patients present with fever, cardiac arrhythmia, vomiting, and altered mental status [1]. Burch and Wartofsky have a predictive scoring system that predicts the likelihood of thyroid storm based on symptoms including fever, altered mental status, gastrointestinal and hepatic dysfunction, tachycardia, heart failure, atrial fibrillation, and a precipitating event. The utility of this scale, however, is limited by its validation in a small population [3, 7]. Thyroid storm has a 10–20% mortality rate and requires rapid identification and treatment [1]. Treatment of thyroid storm should take place in the intensive care unit with a multidisciplinary team and involves inorganic iodine, high-dose corticosteroids, antithyroid drugs, beta-blockers, Tylenol, and external cooling [1, 3, 7].

Graves' Disease

Graves' disease is the most common cause of hyperthyroidism accounting for over 80% of cases with 20–30 cases per 100,000 people [2, 7]. It is six to seven times more common in females than in males with a lifetime prevalence of 3% in females compared to 0.5% in males. While Graves' disease can occur at any age, it is most common in the third and fourth decade of life. It is also commonly triggered after pregnancy [2]. Graves' disease is thought to occur in genetically susceptible individuals following an environmental trigger, which leads to the development of antibodies against the thyroid-stimulating hormone receptor [2, 7]. These antibodies activate the thyrocytes stimulating thyroid hormone production and thus resulting in elevated levels of thyroid hormone (Fig. 1) [2]. Environmental triggers include smoking, pregnancy, immune reconstitution, increased iodine intake, allergic rhinitis,

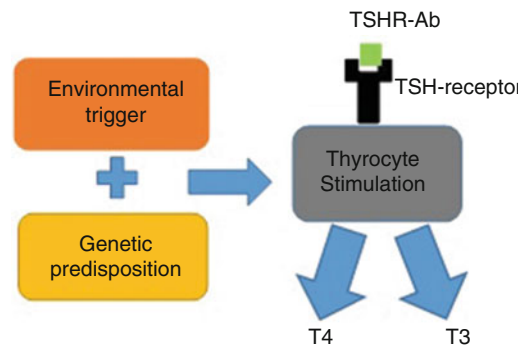


Fig. 1 Pathophysiology of Graves' disease. An environmental trigger in a genetically predisposed individual results in the formation of TSH receptor antibodies which stimulate the TSH receptor resulting in production of T4 and T3 by the thyrocyte

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vitamin D deficiency, and infections, in particular *Yersinia enterocolitica* which mimics the TSH receptor [2, 7].

Clinical Presentation

While symptom onset is gradual, 80% of patients will be symptomatic at presentation. Common symptoms include weight loss, fatigue, anxiety, restlessness, heat intolerance, palpitations, shortness of breath, insomnia, menstrual irregularities, hair loss, hyperreflexia, hypertension, and edema. Some patients will also have signs and symptoms associated with Graves' ophthalmology, which is discussed in further detail below [2].

Diagnostic Workup

Patients with Graves' disease will have undetectable TSH levels in conjunction with elevated T4 and/or T3 levels. TSH receptor antibodies can be detected in several ways; however, many utilize a TPO antibody assay which is over 90% sensitive [2]. Radionuclide uptake scan will show diffuse increased uptake [3]. Thyroid ultrasound has little utility in the workup of Graves' disease. Workup should also include a pregnancy test if applicable and EKG. For treatment planning, one should consider checking a CBC. If a CMP is obtained, individual may note a mildly elevated alkaline phosphate and other liver function tests as well as hypercalcemia [2].

Treatment

The goal in the treatment of Graves' disease is to revert to a euthyroid state as quickly as possible while controlling the symptoms associated with thyrotoxicosis. Beta-adrenergic blockade can be used to decrease conversion of T4 to T3 resulting in lower heart rate, decreased shortness of breath, decreased fatigue, and improved overall functioning. If a patient is unable to tolerate a beta-blocker, verapamil or diltiazem can be utilized [3]. There are three different modalities that can be utilized to revert to a euthryoid state: antithyroid drugs (ATDs), radioiodine, and surgery.

Antithyroid Drugs

Antithyroid drugs (ATDs) are gradually gaining popularity in the USA and are the treatment of choice outside of the USA. ATDS are most likely to be successful in achieving long-term remission in women, those with mild disease, and small goiter. It is the preferred treatment in elderly and high-risk patients, pregnancy, those needing rapid disease control, and those with moderate to severe Graves' orbitopathy. The most common reason for ATD treatment failure is nonadherence [3].

There are two options of ATDs available within the USA, methimazole and propylthiouracil (PTU). Methimazole and PTU act as a substrate for thyroid peroxidase thereby inhibiting the metabolism of iodine and iodination of tyrosine residues needed to make thyroid hormone. They have no effect on T4 or T3 that has already been released from the thyroid, although PTU does decrease conversion of T4 to T3 in the periphery [7]. Methimazole is usually the agent of choice given its better efficacy, longer half-life and duration of action resulting in fewer daily doses, and more favorable side effect profile [3, 7]. The exception to this is in first trimester pregnancy, when PTU is the preferred agent [7]. This is discussed in further depth in the special populations section below.

Initially, a dose of 10–30 mg daily of methimazole is often needed to render a patient euthyroid with continued 5–10 mg thereafter for maintenance dosing. In severe cases twice daily dosing may be needed initially. Higher doses are often needed for more elevated levels of free T4. PTU dosing usually starts between 50 and 150 mg two to three times daily with maintenance dosing 50 mg two to three times daily [3]. Free T4 and total T3 should be monitored every 2–6 weeks after initiation and dose adjustment of ATDs. TSH is not a reliable marker of treatment efficacy as it can remain suppressed for months despite normalization of free T4 and T3. Once a patient is rendered, euthyroid dosing may be decreased 30–50% with continued lab monitoring every 4 to 6 weeks then 2–3 months once stable. Once a patient

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has been stable on treatment for 12–18 months, TSH and TRAb may be checked, and if normal, treatment may be discontinued. If not normal continued low-dose ATD vs. radioactive iodine or thyroidectomy should be considered. Remission is defined as persistent normal TSH, free T4, and total T3 1 year after discontinuing ATD therapy. Following remission TSH should be monitored annually. Remission rates are lower in males, smokers, patients with large goiters, and patients with elevated TRAb levels [3].

In general, ATDs are well tolerated with 5–13% of patients reporting minor side effects such as pruritus, minor rash, arthralgia, and gastrointestinal distress [3, 7]. At low doses 17% of patients discontinue methimazole therapy, whereas 29% discontinue on high-dose methimazole and 34% discontinue on PTU [3]. In rare cases, severe side effects may develop including agranulocytosis, hepatotoxicity, and vasculitis. The vasculitis is an ANCA antibody associated small vessel vasculitis, which while rare is most commonly seen with PTU and presents with fever, arthralgia, and vasculitis with potential renal or pulmonary involvement [3, 7]. The vasculitis usually resolves with drug discontinuation [3].

Agranulocytosis, defined as an absolute granulocyte count less than 500 cells per mm^3, is a rare but potentially life-threatening complication. It has an annual incidence of 0.1–0.3% annually but a 4% mortality rate. It manifests with fever and sore throat and sometimes chills, diarrhea, or myalgia often within the first 90 days of ATD initiation. Any patient on ATDs who develops these symptoms should immediately stop their ATD and obtain a CBC with differential. If their white blood cell count is less than 1000, treatment should be discontinued. Current guidelines recommend a CBC prior to initiation of ATDs, but do not recommend routine surveillance after initiation unless symptomatic [3, 7].

Hepatotoxicity, defined as elevation in liver transaminases more than three times the upper limit of normal, is a rare complication occurring in 0.4–2.7% of patients. It can occur with both methimazole and PTU but is more common and more severe with PTU [3, 7]. Methimazole most often causes a cholestatic pattern of hepatocellular injury, whereas PTU can result in fulminant hepatic necrosis. Higher rates of fulminant liver failure due to PTU are seen in pediatric patients resulting in an FDA warning against its use in this population [3]. Liver failure most commonly occurs within the first 3 months of treatment initiation and peaks within 30 days [7]. It occurs at an average daily dose of 25 mg for methimazole and 217 mg for PTU [3]. Guidelines recommend checking liver function tests at baseline and thereafter if patients show signs of liver failure such as pruritic rash, jaundice, light-colored stools, or dark urine [3, 7].

Radioactive Iodine

Radioactive iodine (RAI) has historically been the treatment of choice for Graves' disease within the USA although it is less often used in other countries [3]. It is contraindicated in pregnant and breastfeeding mothers or women desiring pregnancy in the next 6 months, those with nodules suspicious for malignancy, those unable to comply with safety recommendations, and those individuals with moderate to severe Grave's orbitopathy [3, 7]. In general, radioactive iodine is a safe treatment; however, it can result in a transient exacerbation of hyperthyroidism or in rare cases thyroid storm due to the release of preformed hormone [3]. Some studies have additionally suggested RAI can worsen Graves' orbitopathy. Patients with mild to moderate Graves' orbitopathy can still be treated with radioactive iodine, but should be pretreated with steroids. Individuals with moderate to severe Graves' orbitopathy should avoid radioactive iodine. Additionally, radioactive iodine rarely can precipitate acute thyroiditis. This occurs in less than 1% of cases and can usually be managed with nonsteroidal anti-inflammatories alone or steroids if severe [7].

Consider beta-adrenergic blockade prior to radioactive iodine to help prevent a transient exacerbation [3]. In elderly individuals or individuals with severe symptoms, consider pretreatment with ATDs. Methimazole is the preferred agent and should be held 3–5 days prior to radioiodine treatment and restarted 3–7 days posttreatment. ATDs should be continued until thyroid function normalizes [3, 7]. Beta-blockade can be discontinued when free T4 reaches a normal level [3].

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Following RAI it is recommended to check a TSH at 4–8 weeks and continue repeating every 4–6 weeks until normalized [3, 7]. About 48–77% of patients are rendered hypothyroid after RAI and should be initiated on thyroid replacement [8, 9]. Once rendered euthyroid patients should continue annual thyroid screening for their lifetime [3]. Radioactive iodine can be repeated at 3–6 months if patients fail to respond completely or relapse [3, 7].

Thyroidectomy

While often not utilized as first line treatment, in certain situations, such as patients with a large goiter, greater than 80 g, or large nodules, greater than 4 cm, patients with low radioiodine uptake, patients with suspected cancer, coexisting hyperparathyroidism, moderate to severe Graves' ophthalmopathy or patient preference, thyroidectomy can be the preferred treatment for hyperthyroidism. Prior to surgery, patients should be rendered euthyroid with ATDs and started on beta-blockers to reduce the risk of thyroid storm. Postoperatively patients should be initiated on levothyroxine with weight-based dosing (1.6 μg/kg daily with lower dosing in the elderly). TSH levels should be rechecked 6–8 weeks postoperatively [3, 7]. When performed by a high volume surgeon, complications of surgery are rare at 1–3% with the most common complications being hypocalcemia secondary to permanent hypoparathyroidism and permanent recurrent laryngeal nerve injury [7].

Special Populations

Pregnancy

Graves' disease is the most common cause of hyperthyroidism in pregnancy affecting 5.9 per 1000 pregnancies annually. Risk of Graves' disease is highest in the first trimester and decreases throughout pregnancy. Women see a second peak in Graves' disease 7–9 months postpartum. A diagnosis of Graves' disease in pregnancy is made based on thyrotoxicosis and the presence of TPO antibodies. TSH receptor antibodies can cross the placenta and affect fetal thyroid function. Antibody levels should be assessed at 18–24 weeks and 30–34 weeks. If high levels of antibody are detected the neonate should be monitored for hyperthyroidism [3, 7].

Other causes of hyperthyroidism in pregnancy include gestational thyrotoxicosis and transient subclinical hyperthyroidism. Gestational thyrotoxicosis is a benign, transient condition in which human chorionic gonadotropin affects thyroid production, but no thyroid antibodies are present. This conditions is usually self-limited and only requires treatment if the patient becomes symptomatic [3, 7]. A small percentage of pregnant women will also have subclinical hyperthyroidism (elevated TSH with normal T4 and T3). This is thought to be secondary to changes in pregnancy and does not require treatment [7].

PTU is the preferred agent in the first trimester of pregnancy followed by methimazole in the second and third trimester. In the first trimester, methimazole has been associated with increased risk of aplasia cutis, choanal atresia, esophageal atresia, and omphalocele. While PTU is also associated with birth defects such as preauricular sinuses and cysts and urinary tract abnormalities, these are less severe than the defects associated with methimazole, and thus it is the preferred agent. Following the first trimester, methimazole has been shown to be safe and becomes the preferred agent secondary to the hepatotoxic risk associated with PTU. In pregnancy PTU is often started at a 50–300 mg daily dose and methimazole at 5–15 mg daily dose. PTU dosing can be converted to methimazole using a 10–15 mg PTU to 1 mg methimazole ratio. TSH should be monitored 2 weeks after dosing changes and every 2–6 weeks throughout pregnancy. Pregnancy adjusted TSH, and T4 levels should be utilized as levels in pregnancy can be 150% higher than nonpregnancy levels. As radioactive iodine is contraindicated in pregnancy, if ATDs do not adequately control thyroid levels, thyroidectomy is the preferred treatment modality and is usually completed in the second trimester [3, 7, 10].

Lactating Mothers

Both methimazole and PTU are found in small amounts in breast milk. For lactating mothers,

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methimazole and PTU are both safe to be taken up to 20 and 300 mg daily, respectively; however, methimazole is the preferred agent [3, 7]. Medication should be dosed immediately after feeding [7]. Beta-blockers can be utilized to help manage symptoms with metoprolol and propranolol being the preferred agents in lactating mothers [3].

Pediatrics

Methimazole is the treatment of choice for pediatric patients with Graves' disease. PTU is not routinely used due to the high risk of hepatotoxicity (1 in 2000 to 4000 patients). RAI may be considered in patients over the age of 5 as well as thyroidectomy; however, these treatments are associated with high risk of permanent hypothyroidism [3].

Graves' Ophthalmopathy

Graves' ophthalmopathy is a unique finding found only in patients with hyperthyroidism secondary to Graves' disease [2]. Up to 40–50% of patients with Graves' disease will have some evidence of Graves' ophthalmopathy with 5% having moderate to severe disease. Risk factors for Graves' ophthalmopathy include smoking, untreated or delayed treatment of hyperthyroidism, high thyroid receptor antibody levels, and radioiodine therapy [2, 3]. TSH receptor antibodies stimulate orbital fibroblasts resulting in the production of inflammatory cytokines, hyaluronan, and glycosaminoglycans resulting in muscle and connective tissue volume expansion within the orbit [2].

Clinical Presentation

Graves' ophthalmopathy can result in ocular discomfort and irritation, dry eyes, photophobia, diplopia, reduced color perception, visual field loss, restricted eye movement, and anterior proptosis of the eye. Prolonged exposure can result in keratitis and corneal ulcers. Symptoms usually occur bilaterally; however, severity can be asymmetric. Physical exam may reveal eyelid retraction with bright-eyed stare, periorbital edema, conjunctival erythema, proptosis, chemosis, and restricted eye movements [2].

Diagnosis and Treatment

If the diagnosis of Graves' ophthalmopathy is uncertain or if findings are not symmetric consider CT or MRI for further evaluation to rule out an orbital tumor, CT or MRI will demonstrate enlarged extraocular muscle and increased orbital fibroadipose tissue. Treatment of Graves' disease can improve Graves' ophthalmopathy, but once present, it is not curable. Treatment is best managed in conjunction with endocrinology and ophthalmology and includes prompt restoration to a euthyroid state usually through the use of antithyroid drugs and sometimes steroids, smoking cessation, and symptomatic treatment including utilizing sunglasses, artificial tears, and taping the eyes shut in the evening [2, 3].

Toxic Adenoma

Another cause of hyperthyroidism is toxic adenoma. Toxic adenomas are well-encapsulated, homogenous neoplasia, which secrete thyroid hormone independent of TSH and the rest of the thyroid gland. In iodine-rich areas, toxic adenomas are relatively rare, but they are a leading cause of hyperthyroidism in iodine-deficient areas. Toxic adenomas are more common in women. They can occur at any age but are most common between the age of 30 and 60 years. While usually there is a single hyperfunctioning nodule, at times individuals may have multinodular goiters with multiple functioning nodules. This most commonly occurs in older individuals who are iodine deficient. Exam will often reveal a palpable nodule and possibly a goiter. A radioiodine uptake scan will reveal avid uptake within the nodules with decreased uptake in the surrounding tissue [7]. Treatment of choice is ablative surgery or radioiodine ablation [3, 7]. Lobectomy results in a less than 1% treatment failure rate and a 2–3% risk of permanent hypothyroidism, whereas RAI has a 6–18% treatment failure rate and a 7.6% risk of permanent hypothyroidism at 1 year and a 46% risk of hypothyroidism at 10 years [3].

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Thyroiditis

Thyroiditis is inflammation of the thyroid that results in thyrotoxicosis without hyperthyroidism as thyroid hormone levels are elevated due to the release of preformed thyroid hormone rather than increased production and release [2, 7]. It can be characterized by its time course as acute or subacute. Causes of acute thyroiditis include infectious thyroiditis, radiation thyroiditis, and traumatic thyroiditis. Causes of subacute thyroiditis include subacute thyroiditis, silent thyroiditis, and drug-induced thyroiditis [2].

Causes of Acute Thyroiditis

Infectious Thyroiditis

Infectious thyroiditis is a very rare condition accounting for only 0.1–0.7% of thyroid disease, which results in an acute painful neck swelling, fever, sore throat, dysphagia, dysphonia, desire to keep head flexed, and potentially systemic symptoms of infection due to a bacterial or fungal infection of the thyroid. Rapid identification and treatment is essential as infectious thyroiditis can have severe complications including sepsis, neck compression, necrotizing mediastinitis or pericarditis and even death. While infection of the thyroid is rare, the following conditions put individuals at increased risk: piriform sinus tract fistula, third and fourth brachial arch abnormalities, operative manipulation (thyroid lobectomy or biopsy, central line placement), intravenous drug use, immunocompromised states, endocarditis, tooth abscess, and esophageal perforation or rupture [2, 6].

The infection is usually polymicrobial with both gram-positive bacteria, most commonly *Staph. aureus or Streptococcus pyogenes*, *Streptococcus epidermidis*, or *Streptococcus pneumoniae*, and gram-negative aerobes, most commonly *E. coli*, and anaerobes, most commonly *Clostridium septicum*, Gram-negative bacilli, and peptostreptococcus, present. Rarely fungi or parasitic infections may also be present. In patients with a more subacute or chronic presentation that may mimic carcinoma or a multinodular goiter, mycobacterium tuberculosis should be suspected [2, 6].

Workup for infectious thyroiditis should include CBC, inflammatory blood markers, TSH, and evaluation for sepsis if warranted. HIV testing should also be considered. Patients may be euthyroid or hyperthyroid due to release of preformed hormone on presentation. Ultrasound should be obtained to evaluate for abscess or aggressive cancer mimicking infection. A CAT scan with intravenous contrast can also be considered to better evaluate the extent of the infection. A barium swallow can be obtained if a fistula is suspected. An FNA should be utilized to obtain a culture to direct antibiotic therapy [2, 6].

The patient should initially be started on broad-spectrum intravenous antibiotics and deescalated based on culture. Percutaneous drainage should also be considered if an abscess is present. If a fistula is present, individuals are at risk of recurrence and the fistula should be surgically removed once stable. Infectious thyroiditis has a 12% mortality rate if untreated. For those who survive, their prognosis is excellent with only a small number developing permanent hypothyroidism [2, 6].

Radiation Thyroiditis

Radiation exposure to the anterior neck can result in inflammation of the thyroid and release of preformed hormone. Radiation thyroiditis is seen in 1–5% of patient who undergo radioactive iodine, with those being treated with higher doses for cancer more susceptible than those treated for hyperthyroidism. Patients may experience anterior neck pain and swelling within a few days or up to 2 weeks following radiation. In severe cases thyroid storm may be elicited. Treatment is usually symptomatic with NSAIDs or steroids if symptoms are severe [2].

Traumatic Thyroiditis

Traumatic thyroiditis is direct anterior neck pressure or manipulation that results in the release of preformed thyroid hormone resulting in thyrotoxicosis. It often is self-limited and goes unrecognized and unreported. It most often occurs after parathyroidectomy. It usually does not result in pain. If patients are symptomatic, they can be treated with corticosteroids [2].

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Causes of Subacute Thyroiditis

Silent Thyroiditis

Silent or sporadic painless thyroiditis is a painless, subacute lymphocytic inflammation of the thyroid in nonpregnant patients that results in the release of preformed hormone resulting in thyrotoxicosis [3]. Silent thyroiditis has an incidence rate of 1–10%. It is most commonly seen in females between the age of 30 and 50 years of age. Often patients have no known preexisting thyroid disease [2]. It is triggered by medications such as lithium, interferon-α, tyrosine kinase inhibitors, monoclonal antibodies, interleukin therapy, and amiodarone. Trauma, autoimmune triggers, and hormone fluctuations such as those that occur after adrenalectomy, steroid cessation, or in Addison's disease or hypopituitarism can also trigger silent thyroiditis. For some patients, no cause or trigger can be identified [2, 3].

Silent thyroiditis often follows a similar triphasic course as seen in postpartum thyroiditis with a hyperthyroid phase followed by a hypothyroid phase and finally resolution to a euthyroid state. About 5–20% will be thyrotoxic at diagnosis with symptoms such as palpitations, anxiety, and tremor. Symptoms are usually relatively limited and less severe than those seen in Graves' disease. The thyrotoxic phase lasts approximately 3 months and is often followed by a hypothyroid phase for 3–6 months before returning to a euthyroid state usually within 1 year of disease onset. About 10–20% of patients with silent thyroiditis will go on to develop permanent hypothyroidism. Ultrasound of the thyroid will reveal a hypoechogenic appearance with low radioiodine uptake on uptake scan.

Treatment during the thyrotoxic phase is symptomatic only with beta-blockers. As the thyrotoxic phase is due to release or preformed hormone and not ongoing production, ATDs have no role in treatment. The hypothyroid phase can be monitored if symptoms are mild. If symptoms increase in severity patients should be treated with levothyroxine for 6–12 months after which it can be discontinued and monitored for recovery to a euthyroid state. About 5–10% of patients will have a recurrent episode of silent thyroiditis [2].

Postpartum Thyroiditis

Postpartum thyroiditis is an autoimmune, destructive thyroiditis that occurs within 1 year postpartum or following a miscarriage. It has been proposed that postpartum thyroiditis occurs due to postpartum hormonal and immunological rebound [2]. Up to 10% of women will experience postpartum thyroid dysfunction [3].

It is important to differentiate the thyrotoxic phase of postpartum thyroiditis, a transient condition, from Graves' disease, a permanent condition. Postpartum thyroiditis is 20 times more common than Graves' disease in this population [2]. Postpartum thyroiditis is usually painless. It is more common in individuals with a personal or family history of autoimmune disorders, smoking, and individuals with antithyroid peroxidase antibodies [3].

Postpartum thyroiditis classically has a triphasic course with a transient hyperthyroid phase followed by a 1- to 6-month hypothyroid phase and resolution to euthyroid. While this is the classic presentation, only 24–28% of patients experience all three phases with 43–50% only experiencing hypothyroidism and 24–32% only experiencing hyperthyroidism [2, 3].

Diagnostic Evaluation

Antithyroid peroxidase antibodies and thyroglobulin antibodies may be elevated [2, 3]. The ratio of T4 to T3 is usually less than 20 ng/μg, whereas Graves' disease results in a ratio greater than 20 ng/μg [3]. Radioactive iodine uptake scan will show decreased uptake. Ultrasound will show hypoechogenicity [2].

Treatment

ATDs are usually not indicated as the hyperthyroidism is transient. Beta-blockers can be utilized for symptomatic management with metoprolol and propranolol being the preferred agents if breastfeeding [2, 3]. The hypothyroid state can be treated with thyroid hormone replacement if patients are symptomatic, planning pregnancy or breastfeeding. Treatment can usually be withdrawn at 1 year. TSH should continue to be monitored. Some women will have persistent hypothyroidism. Women who are multiparous,

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older have higher TPO antibodies, higher TSH at diagnosis, and increased hypoechogenicity on ultrasound are at increased risk of permanent hypothyroidism [2]. Women who have experienced postpartum thyroiditis are at increased risk of experiencing it again following subsequent deliveries with some studies showing up to a 70% recurrence rate [2, 3]. Patients are also at increased risk of developing Graves' disease in the future [3].

Subacute Painful Thyroiditis

Subacute thyroiditis, also known as De Quervain thyroiditis or subacute granulomatous thyroiditis, results in fever and moderate to severe pain over the thyroid that radiates to the ears, jaw, and throat. Patients may also complain of fatigue and malaise, anorexia, arthralgia, and myalgia. The thyroid may be enlarged and firm [2, 3, 6]. Initially the inflammation results in damage to follicles resulting in the release of preformed thyroid hormone. In response to the influx of thyroid hormone, TSH inhibition decreases production of new thyroid hormone. As the inflammation resides, the thyroid regenerates, and the patient returns to a euthryoid state [2]. Subacute thyroiditis has an incidence of 1.8% and is more common in females [6]. Incidence peaks in the fifth decade of life. Subacute thyroiditis has a strong association with HLA-B35 and HLA-B67 [2]. It is often triggered by a virus, and patients often have upper respiratory symptoms prior to onset [3, 6]. Several viruses have been linked to subacute painful thyroiditis including mumps, influenza, adenovirus, measles, mononucleosis, coxsackievirus, enterovirus, echovirus, Epstein-Barr virus, cytomegalovirus, hepatitis E, dengue fever, rubella, HIV, and cat scratch fever [2, 6]. Inflammatory markers such as ESR and CRP may be elevated. Patient may also have a mild leukocytosis. Up to 25% may have mild elevation in antithyroid antibodies. Ultrasound if obtained will demonstrated diffuse heterogenicity with focal hypoechoic areas and decreased or normal color flow on Doppler. Radioiodine uptake scan will show diffuse low uptake levels. Most cases are transient with a 3- to 6-month thyrotoxic phase followed by hypothyroidism in 30%. Only 60% are symptomatic in the hyperthyroid phase at presentation. For the majority of patients, the hypothyroid phase is mild and asymptomatic. Most return to a euthyroid state over 6–12 months, but up to 5–15% will have persistent hypothyroidism [2, 3]. Patients who have experienced subacute thyroiditis are at increased risk for late-onset permanent hypothyroidism and Graves' disease in the future [2]. Treatment is supportive with NSAIDs and beta-blockers. If not well controlled with these measures, a corticosteroid taper over 4–6 weeks can be utilized [2, 3, 6].

Drug-Induced Thyrotoxicosis

Medications can result in thyroid dysfunction. One medication commonly associated with this is amiodarone, which results in thyrotoxicosis in up to 5–10% of users [3, 7]. Amiodarone can result in an overproduction and release of thyroid hormone due to the high iodine content or it can have a direct toxic effect on thyrocytes resulting in release of preformed thyroid hormone [7]. If this occurs amiodarone should be discontinued. Corticosteroids can also be considered. Because of the high risk of thyrotoxicosis, it is recommended that all patients started on amiodarone be screened with TSH for thyroid dysfunction within 3 months of treatment initiation and every 3–6 months thereafter [3]. Other medications associated with thyroid dysfunction include lithium, tyrosine kinase inhibitors, and interferon [2].

Secondary Hyperthyroidism

Secondary hyperthyroidism is rare but occurs when elevated or inappropriately normal levels of TSH result in overproduction of thyroid hormones. This is most often the result of a TSH producing pituitary adenoma and can be further evaluated with an MRI of the pituitary gland [3].

Factious Ingestion

At times, individual may take thyroid hormone replacement unbeknownst to their provider. This results in low TSH levels with elevated T3 and T4

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levels with a ratio less than 20 and nearly no radioiodine uptake on radioiodine uptake scan [3].

Rare Causes

Rare causes of hyperthyroidism include thyrotropin-induced thyrotoxicosis, euthyroid hyperthyroxinemia secondary to thyroid-binding protein disorders, and trophoblastic tumors [3, 7]. These conditions are beyond the scope of this review and patients should be referred to endocrinology if they are suspected.

Subclinical Hyperthyroidism

Up to 1.8% of the population will have evidence of subclinical hypothyroidism defined as a TSH below the lower limits of normal with normal T3 and T4 levels. The majority of patients will revert to normal levels without intervention within 5 years; however, 0.5–7% will progress to overt hyperthyroidism. Guidelines recommend rechecking TSH at 2–6 weeks and if persistently low repeat every 3–6 months. If TSH is persistently low greater than 6 months and the patient is elderly, at increased cardiac risk, diagnosed with osteoporosis or symptomatic consider treatment with thyroid hormone replacement. If they do not meet any of these criteria, continued observation is warranted [3].

Summary (Table 2)

Thyroid Nodule

Thyroid nodules are exceedingly common in the general population with 4–7% of the population with palpable nodules identified on physical exam [11] and up to 50–76% of the population having nodules identified on clinical imaging or autopsy [10, 11]. With an annual incidence rate of 0.1%, there will be over 350,000 new nodules identified in the USA over the next year. The risk of having a thyroid nodule increases with age and is four times more common in women than men [11]. Fortunately, the vast majority of these nodules are benign and asymptomatic [10]. Nodules have an increased likelihood of being malignant in individuals with a history of head and neck radiation, a personal or family history of thyroid cancer, and in particular medullary thyroid cancer or multiple endocrine neoplasia (MEN) syndrome, age less than 14 years or greater than 70 years, males, and if symptoms are present [10, 11]. When nodules are symptomatic, they may result in a choking sensation, cervical tenderness, dysphagia, or dysphonia, although, the presence of these symptoms does not necessarily indicate the presence of a thyroid nodule as these most often are the results of a different etiology [10]. Routine suppression of thyroid nodules with thyroid hormone replacement is not warranted given the high risk of side effects and limited efficacy in trials [10].

Evaluation

Laboratory Studies

A TSH level should be evaluated in all individuals with a thyroid nodule. If TSH levels are normal, no further testing is needed. If TSH levels are elevated, a free T4 and TPO antibodies should be obtained to evaluate for Hashimoto's thyroiditis. If TSH levels are low, a patient should be further evaluated with free T4, total T3, and thyroid scintigraphy. Thyroid scintigraphy can also be helpful in multinodular goiter as hyperfunctioning nodules have a very low risk of malignancy [11] and do not warrant fine needle aspiration (FNA) unless they have suspicious features [10]. If the above criteria are not met, thyroid scintigraphy has little utility in the evaluation of a thyroid nodule [10].

Imaging

Any palpable nodule or nodule visualized on other imaging modalities (CT scan, MRI, or PET scan) should be further evaluated with a dedicated thyroid ultrasound [10]. Nodules detected on PET scan have a high risk of malignancy with over 82% of nodules being malignant [11]. Nodules identified on PET scan should be further evaluated with

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Table 2 Summary of etiology of thyrotoxicosis, cause, diagnostic findings, and treatment

Etiology	Cause	Diagnostic findings	Treatment
Graves' disease	TSH-R Ab	TSH-R AB	ATDS, thyroidectomy or radioactive iodine
		TPO-AB	
		TG-AB	
		T4:T3 >20 ng/μg	
		Increased radioactive iodine uptake	
Toxic adenoma	TSH-independent hyperfunctioning nodule(s)	Palpable nodule or goiter on exam	Surgical excision or radioactive iodine ablation
		Avid, localized uptake with decreased uptake in the surrounding tissue on radioiodine uptake scan	
Infectious thyroiditis	Bacteria or fungal infection	Fever + painful thyroid + systemic symptoms	Broad-spectrum antibiotics. Percutaneous drainage if abscess. Remove fistula if present
		Leukocytosis, elevated ESR, CRP	
		Ultrasound or CT scan may demonstrate abscess	
		Barium swallow may demonstrate fistula	
		FNA culture for infectious agent	
Traumatic thyroiditis	Trauma, neck surgery, or pressure	Non-tender self-limited thyrotoxicosis	Usually self-limited
			Steroids if symptomatic
Silent thyroiditis	Medications, autoimmune, trauma, idiopathic	Painless thyroid Thyroid antibodies may be present Triphasic course Ultrasound hypoechogenic Low radioiodine uptake	Thyrotoxic phase-symptomatic treatment Hypothyroid phase-levothyroxine if moderate to severe symptoms
Postpartum thyroiditis	Postpartum (within 1 year) immunological rebound	Triphasic course APO-AB TG-AB T4:T3 <20 ng/μg Ultrasound hypoechogenic Low radioiodine uptake	Thyrotoxic phase-symptomatic treatment Hypothyroid phase-levothyroxine if symptomatic, planning pregnancy or breastfeeding
Subacute painful thyroiditis	Viral trigger	Fever + pain over thyroid Elevated ESR, CRP, leukocytosis Ultrasound diffuse heterogenicity with focal hypoechoic areas Diffuse decreased uptake on radioiodine uptake scan	Mild to moderate-beta-blocker and NSAID Severe corticosteroids
Drug induced	Lithium, interferon, amiodarone, monoclonal antibodies, tyrosine kinase inhibitors	Painless thyrotoxicosis	Discontinue offending agent
Radiation induced	Radiation within last 2 weeks	Anterior neck pain or swelling	Mild-NSAIDS
			Severe corticosteroids
Factious thyrotoxicosis	Inappropriate ingestion thyroid hormone	Low TSH, elevated T4 and T3	Discontinue ingestion of thyroid hormone
		No uptake on radioiodine uptake scan	
Secondary hyperthyroidism	Pituitary adenoma	Inappropriately normal or elevated TSH in setting of elevated T4 and T3 levels	Referral

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both a dedicated thyroid ultrasound and FNA [10]. While there are several classification schemes based on ultrasound findings, the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and the Associazione Medici Endocrinologi (AME) recommend categorizing thyroid nodules as low, intermediate, or high risk for malignancy [10, 11] with further workup based on these classifications (Table 3, Fig. 2).

If an FNA is warranted, it should be performed by an experienced clinician as this increases

Table 3 Thyroid nodule characterization and treatment and follow-up recommendation based on risk categorization by ultrasound [10, 11]

Risk categorization	Ultrasound characteristics	Malignancy risk	Obtain FNA if size
Low risk	Thyroid cysts	<1%	>20 mm or growing
	Mostly cystic (>50%)		
	Isoechoic spongiform nodule		
Intermediate risk	Slightly hypoechoic	5–15%	>10 mm
	Central vascularity		
	Macrocalcifications		
	Indeterminate hyperechoic spots		
	Ovoid to round		
	Smooth or ill-defined margins		
	Elevated stiffness		
High risk	Markedly hypoechoic	50–90%	>5 mm
	Microcalcifications		
	Irregular speculated, microlobulated margins		
	Taller than wide		
	Extracapsular/thyroidal extension		
	Pathologic adenopathy		

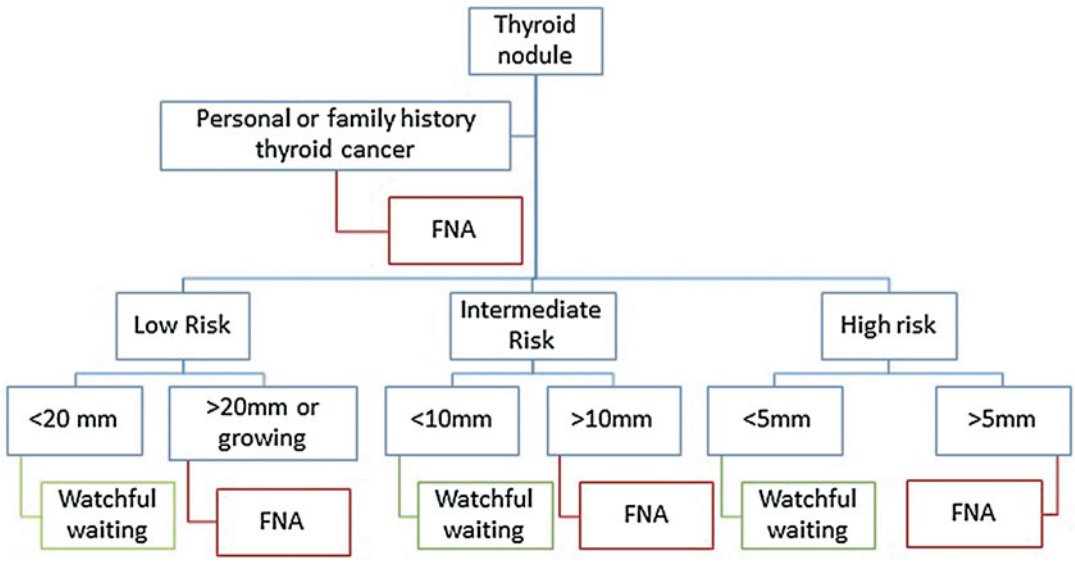


Fig. 2 Summary of thyroid nodule diagnostic workup based on risk categorization as outlined by the American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), and the Associazione Medici Endocrinologi (AME) guidelines

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sensitivity to 97.0%, specificity to 50.5%, and diagnostic accuracy to 68.8% and decreases the risk of false-negative and nondiagnostic results [10]. False negatives can further be reduced to 1–6% through the use of ultrasound to guide biopsy location, the aspiration of at least two sites within the nodule, and evaluation and interpretation by an experienced cytopathologist [10, 11]. If a suspicious lymph node is identified on ultrasound, it should also be biopsied. A sample is considered diagnostic if greater than six groups of well-preserved thyroid epithelial cells with at least ten cells per group [10]. AACE/ACE/AME categorize thyroid nodules into five distinct cytological classifications which are heavily based on the Bethesda System for Reporting Thyroid Cytopathology: nondiagnostic, benign, indeterminate, suspicious, and malignant [10, 11] (Table 4).

A sample is considered to be nondiagnostic when the sample contains fewer than six groups of well-preserved thyroid epithelial cells with at least ten cells per group. If a sample is nondiagnostic but appears cystic and there are no concerning clinical or ultrasound features, the nodule can be followed conservatively with follow-up in 1 year for clinical exam and ultrasound. If it is stable, ultrasound and clinical exam should be repeated after 24 months. If a nodule appears solid and is nondiagnostic, an FNA biopsy should be repeated at least 1 month from the original biopsy [10]. Up to 50% of repeat FNA biopsies will remain nondiagnostic [11], and as there is a 2–16% malignancy rate, surgical excision should be considered at that time [10].

The most common cytopathology classification is benign. These nodules have a low risk of malignancy. If clinical and ultrasound findings are favorable and the patient is asymptomatic, no further workup is necessary. If the nodule is benign with favorable clinical and ultrasound findings, but symptomatic, it can be followed conservatively as described above. Finally, if biopsy results return as benign; however, the ultrasound shows concerning features, the nodules increases its volume by more than 50% in 1 year, or it becomes symptomatic a repeat FNA biopsy should be obtained. If symptoms persist surgical intervention, image-guided thermal ablation or percutaneous ethanol injections can be considered [10]. Furthermore, all nodules greater than 3–4 cm should be evaluated for surgical excision regardless of FNA findings as there is an increased risk of false-negative results [10, 11].

About 10–25% of FNA biopsies will return as indeterminate. This is a difficult group to manage given high variability in malignancy rates. Due to these complicating factors, referral to a specialist should be considered. The AACE/ACE/AME have recommended subdividing this group into low-intermediate and high-risk groups to better

Table 4 AACE/ACE/AME cytopathology classification of thyroid nodules, risk of malignancy, and diagnostic workup [10]

Cytopathology classification	Rate of result	Malignancy risk	Workup
Nondiagnostic	<10%	2–16%	If cystic or predominantly cystic and no suspicious US features conservative management[a]
			If solid repeat FNA. Surgical excision if persistently nondiagnostic unless favorable US and clinical factors
Benign	54–54%	0–3.7%, expertise centers <1%	If no suspicious US features and asymptomatic no further workup
			If no suspicious US features but symptomatic conservative management
			If suspicious US or increase in volume >50% in 1 year, or becomes symptomatic repeat FNA
Indeterminate	10–25%	Low risk 5–15%	Conservative management, consider elastography
		High risk 15–30%	Lobectomy plus isthmectomy or total thyroidectomy
Suspicious	2.5–5%	70–75%	Total thyroidectomy or lobectomy plus isthmectomy
Malignant	2.7–5.4%	>95%	Total thyroidectomy

[a]Conservative management: clinical exam and US at 12 months and if unchanged repeat at 24 months

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convey the malignancy risk. Nodules in the low-intermediate risk group may be followed with conservative management. Nodules in the high-risk group should be removed with a thyroid lobectomy and isthmectomy. A total thyroidectomy can also be considered but is not required unless malignancy is confirmed. Additionally, all nodules suspicious or confirmed malignant should be removed with surgical excision [10].

Special Populations

There are two special populations in which the above evaluation and treatment scheme for thyroid nodules do not apply. The first is children, in whom the risk of malignancy, diagnosis, and treatment vary widely and thus should be managed if possible in conjunction with a pediatric endocrinologist. In addition, women who are pregnant are at higher risk for developing new thyroid nodules or having an increase in size in a known nodule. Diagnostic workup and treatment, however, are the same as in nonpregnant individuals with the caveat that if surgical excision is needed, it should be performed in the second trimester if possible [10].

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Osteopenia and Osteoporosis

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Katherine Reeve, Anna Meola, and Ryan West

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Osteoporosis is a major health concern worldwide and within the United States. Approximately 9% of US adults over the age of 50 have osteoporosis, and up to 50% have some degree of low bone density [1]. Osteoporosis causes more than two million fractures per year with $19 billion in associated costs in the United States alone [2]. The clinical costs of an osteoporotic fracture are equally great and include increased mortality, increased disability, and an increased need for long-term nursing care. The most common sites of fracture are the hip, vertebrae, and wrist. Hip fractures are particularly deadly, carrying a 26%

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1-year mortality rate for patients over the age of 69. Of those who survive, functional skills are significantly decreased with decreased fine motor and mobility scores [3]. Vertebral fractures lead to chronic back pain and deformity in up to 30% of patients. These fractures may have a long-term impact on overall quality of life and the ability to carry out activities of daily living (ADL).

Osteoporosis is defined as decreased bone mineral density leading to increased fragility and an increased risk of fractures. Symptoms are usually not present early on, and an osteoporotic fracture is often the first sign of disease. The lifetime risk of an osteoporotic fracture is 44% [4].

Osteoporosis can be primary or secondary. Primary osteoporosis is bone loss as a result of aging alone. Secondary osteoporosis refers to bone loss as a result of chronic conditions that lead to accelerated bone loss. It can be caused by endocrine disorders such as hyperparathyroidism or hyperthyroidism. Other causes include malignancy, renal failure, and nutritional deficiencies [5].

Risk Factor Assessment

Risk factor assessment begins with taking a detailed history and performing a physical exam. Risk factors for developing osteoporosis include family history, lifestyle, and contributing medical conditions (Table 1).

Lifestyle

Lifestyle choices can affect bone density. Excessive use of alcohol and cigarette smoking are both associated with increased fracture risk [4]. Regular physical activity early in life is associated with higher peak bone mass, and continued activity leads to lower rates of hip fractures in postmenopausal women [5]. Maintaining healthy eating habits is necessary to obtain the required nutrients to build healthy bone mass. Calcium and Vitamin D are two of these essential nutrients.

Genetics

Several genetic factors can increase the risk of developing osteoporosis. Those of northern European or Asian descent have higher rates of osteoporosis and osteopenia. Women are at a much higher risk of developing osteoporosis than men due to accelerated bone loss after menopause. Certain genetic conditions such as Turner's syndrome increase risk of osteoporosis due to decreased estrogen production.

Endocrine Factors

There are several endocrine disorders that can increase risk of osteoporosis. Any disorder that decreases estrogen production will increase risk. This includes early menopause, surgical menopause, or premature ovarian failure. Risk is also increased by endocrine disorders that disrupt normal bone metabolism, such as hyperthyroidism, hyperparathyroidism, Addison's disease, and Cushing's syndrome.

Medications

Certain medications can have a negative effect on bone metabolism, including anticoagulants, corticosteroids, thyroid hormone, chemotherapeutic agents, anticonvulsants, loop diuretics, proton pump inhibitors, antidepressants, and

Table 1 Risk factors for osteoporosis

Lifestyle	Family history	Genetic/Medical
Poor diet Low activity level Tobacco use Alcohol use Low body weight < 128 lb	History of osteoporosis History of fractures	Menopause Caucasian or Asian ethnicity Endocrine disorders Certain medications

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medroxyprogesterone acetate (MDA). Chronic use of any of these medications may increase the risk of developing osteoporosis and suffering osteoporotic fractures.

There are a few medications associated with increased bone mass and decreased rate of factures, including thiazide diuretics, statins, and beta blockers [6].

Laboratory Assessment

If the history and physical exam suggests secondary causes of osteoporosis, laboratory testing should be considered and must be guided by the patient presentation. Useful initial testing may include thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), calcium, vitamin D, complete blood count (CBC), complete metabolic panel, 24 h urinary calcium, and testosterone in men. To measure vitamin D levels, 25(OH)D should be used, not 1,25-dihydroxyvitamin D (4).

Bone Densitometry Assessment

The most important evaluation for osteoporosis is determining the bone mineral density (BMD). The diagnosis of osteoporosis it made primarily based on the BMD and is defined as a BMD 2.5 standard deviations (SD) below the mean for young Caucasian females.

It is important to determine the BMD of patients who are at increased risk of osteoporosis to identify, prevent, and treat osteoporosis. Using the BMD we can estimate future fracture risk, guide treatment decisions, and monitor response to treatment. Both the US Preventive Services Task Force (USPSTF) and the International Society for Clinical Densitometry (ISCD) have issued recommendations on who should be screened for osteoporosis with BMD testing (see Table 2).

The mostly widely used and universally accepted method of measuring BMD is the dual-energy x-ray absorptiometry (DXA) scan. It has been accepted as the gold standard for determining the BMD of the hip and spine. It has replaced the quantitative computed tomography (CT) scan, which requires significantly greater radiation exposure. The DXA report includes both a T score and a Z score. The T score is defined as the number of standard deviations above or below the mean BMD for a young Caucasian female. The Z score is similar but uses a mean BMD that is adjusted for age, gender, and race.

Although there has been some disagreement in the past, currently both the World Health Organization (WHO) and the ISCD recommend using T-scores as the standard to evaluate all postmenopausal women and men older than 50 [7]. Based on their T-score, patients can be classified into three categories: normal BMD, osteopenia, or osteoporosis. A different classification is recommended for premenopausal women, men under 50, and children. In these cases the Z score should be used instead [8]. Based on their Z score, patients can be classified into two categories: below expected range or within expected range for chronological age with a Z score below or above −2.0 respectively.

Alternative studies exist to evaluate for fracture risk, including quantitative ultrasonography (QUS) and peripheral DXA (pDXA). These modalities are generally less expensive and more portable and may be used in settings where DXA is not available. Both of these may help predict future fractures. However, they cannot be used to reliably determine BMD and should not be used for diagnosis or tracking disease progression if DXA or quantitative CT is available.

FRAX Score

The Fracture Risk Assessment tool (FRAX) was developed in 2008 by the WHO to estimate 10-year probability of hip fracture and major osteoporotic fracture. These estimates are based on untreated patients between 40 and 90 years of age. The calculation uses several risk factors including age, fracture history, steroid use, body mass, smoking, alcohol use, rheumatoid arthritis, parental history of hip fracture, and having secondary causes of osteoporosis. Femoral neck bone mineral density (BMD) can also be factored in if available but is not needed to generate the 10-year

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Table 2 Indications for bone mineral density (BMD) screening

US Preventive Services Task Force[a]	International Society for Clinical Densitometry[b]
Women ≥65	Women ≥65
Women <65 with fracture risk equal to or greater than 65-year-old white female	Women 60–64 with fracture risk equal to or greater than 65-year-old white female
Men: insufficient evidence to determine benefit vs harm	Women on prolonged hormone replacement therapy
	Men ≥70
	Anyone with a fragility fracture
	Anyone receiving or considering treatment for osteoporosis

[a]United States Preventive Services Task Force. Osteoporosis: Screening, 2018
[b]International Society for Clinical Densitometry. Osteoporosis Screening Guidelines, 2012

Table 3 World Health Organization (WHO) Diagnostic criteria for osteoporosis

Diagnosis	Bone Mineral Density (BMD) T score [a]
Normal	≤1
Osteopenia	1–2.5
Osteoporosis	≥2.5

Source: WHO Assessment of Osteoporosis at the primary care level (2004)
[a]Standard deviation (SD) below the mean in healthy young females

risk. There is a calculator available online at www.shef.ac.uk/FRAX. It is often included on DXA reports [11]. This information can help guide management and may indicate the need for earlier treatment in patients with osteopenia (see section "Pharmacological Treatment" below).

Diagnosis

The diagnosis of osteoporosis is made primarily from bone mineral density using DXA as the gold standard for assessment. Osteoporosis in postmenopausal women and in men greater than 50 is defined as bone mineral density 2.5 standard deviations below normal as reflected by a T score of −2.5. Osteopenia is defined as a bone mineral density of 1–2.5 standard deviations below normal with a T score of −1 to −2.5. In premenopausal women and men less than 50 they are considered to be below the expected range for age if the bone mineral density is more than 2.0 standard deviations below normal adjusted for age as reflected by a Z score of −2.0. Alternatively, a clinical diagnosis of osteoporosis can be made in any adult based on the presence of a fragility (low trauma) fracture [9] (Table 3).

Prevention and Treatment

Nonpharmacological

There are several nonpharmacological measures that can be taken to help prevent and treat osteoporosis. These measures include an active lifestyle with weight bearing exercises, fall precautions, avoidance of tobacco and excessive alcohol use, and adequate intake of calcium and vitamin D. These measures should be started early in life and continued. BMD peaks around age 35 and then is slowly lost. This loss is accelerated in women after menopause when estrogen levels drop.

Calcium

The recommended daily intake of calcium for postmenopausal women is 1200 mg/day. For adult men, it is slightly lower at 1000 mg/day [10]. Calcium supplementation is recommended if a sufficient amount cannot be obtained by diet alone. There are different formulations of calcium supplements, citrate and carbonate. Calcium citrate is best absorbed when taken between meals. Conversely, calcium carbonate is best absorbed when taken with meals. No form of calcium should be taken with iron as iron decreases intestinal absorption of calcium. Studies have shown that calcium in combination with Vitamin D can increase BMD and may or may not decrease fracture risk in postmenopausal women

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[11]. Given its mild effect on BMD and fracture risk, supplementation alone is not recommended as monotherapy for osteoporosis.

Vitamin D

Vitamin D assists with calcium absorption. The recommended daily intake of vitamin D needed for adequate calcium absorption is 600–800 IU according to the National Institutes of Health (see Table 4). The National Osteoporosis Foundation (NOF) differs slightly. NOF recommends 400–800 IU for those under age 50 and a higher intake of 800–1000 IU for those over age 50 [12]. Patients with a documented Vitamin D deficiency (<20 ng/mL) or insufficiency (20-29 ng/mL) should be treated with 5000 IU of Vitamin D3 (cholecalciferol) daily for 8–12 weeks followed by a maintenance dose of 1000 IU of Vitamin D3 daily. Supplementation with D3 rather than D2 (ergocalciferol) may be preferable because many laboratory assays do not measure D2 as accurately. The treatment goal is a serum 25(OH)D level greater than 30 ng/mL. Rarely, higher doses (up to 10,000 IU weekly) may be required to achieve adequate levels of vitamin D.

Table 4 Optimal calcium[a] and vitamin D intake[b]

Population	Calcium	Vitamin D
Infants, children, and young adults		
0–6 months	200	400
6–12 months	260	400
1–13 years	700–1300	400–600
14–18 years	1300	600
Adult women		
Pregnant or lactating		
14–18 years	1300	600
19–50 years	1200	600
Other		
51–70 years	1200	600
71+ years	1200	800
Adult men		
19–70 years	1000	600
71+ years	1200	800

Adapted from the National Institutes of Health Recommendations on Calcium and Vitamin D 2019
[a]Calcium recommendations in mg/day
[b]Vitamin D recommendations in IU/day

Physical Activity

Maintaining an active lifestyle with adequate physical activity, particularly weight-bearing exercise is important in maintaining musculoskeletal health. Exercise has been shown to slightly increase BMD and slightly reduce the risk of having a fracture. Weight-bearing activities include but are not limited to walking, climbing stairs, elliptical machines, and resistance training with weights. Maintaining a healthy and active lifestyle may also reduce the risk of falls, which in turn may reduce the risk of fractures [13].

Fall Prevention

Falls cause the majority of osteoporotic fractures. Risk factors for falls are numerous and include visual or hearing impairments, musculoskeletal disorders, cognitive disorders, and advanced age. Many medications can also increase the risk of falls. These include antidepressants, antipsychotics, benzodiazepines, diuretics, beta blockers, and antihypertensives. A detailed history should be obtained on each patient to document fall risks and identify any potentially concerning medications. It may be appropriate to start patients in an exercise program or physical therapy to improve balance and strength or adjust medications to prevent future falls.

Pharmacological Treatment

Pharmacological treatment is the mainstay of osteoporosis management. Available agents for prevention and treatment of osteoporosis include bisphosphonates, calcitonin, hormone therapy, estrogen agonists/antagonists, parathyroid hormone (PTH), the RANK Ligand inhibitor Denosumab, and Romosozumab.

Indications for treatment:

- Diagnosis of osteoporosis
- Diagnosis of osteopenia plus >3% risk of hip fracture or >20% risk of major osteoporotic fracture in 10 years based on FRAX score
- A history of vertebral or hip fractures

The optimal duration of treatment has not been determined. The decision of when to stop

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treatment or consider a drug holiday remains controversial and will depend on the agent used and the severity of disease.

Bisphosphonates

Bisphosphonates are considered first-line therapy for the treatment and prevention of osteoporosis due to high efficacy, low side effects, and reasonable cost [9]. They are available in both oral and intravenous preparations. All of the agents listed below are FDA approved for both the prevention and treatment of postmenopausal osteoporosis except Ibandronate, which is approved for treatment only. The most common side effect from the oral preparations is acid reflux. Therefore patients should be advised to take the medication with a full glass of water on an empty stomach and remain upright for 30–60 min. Osteonecrosis of the jaw is a rare but serious side effect, affecting 1/10,000 to 1/100,000 people each year. This risk is higher with IV than oral bisphosphonates.

Alendronate (Fosamax)

Alendronate reduces the incidence of spine and hip fractures by about 50% over 3 years with or without a history of previous fracture. It is an oral medication. The recommended starting dose for postmenopausal osteoporosis prevention is 5 mg/day or 35 mg/week. Treatment dose is 10 mg/day or 70 mg/week. Weekly dosing may increase adherence as it is simpler and causes less esophageal irritation from acid reflux.

Risedronate (Actonel)

Risedronate reduces the incidence of vertebral fractures by 41–49% and nonvertebral fractures by 36% over 3 years. It is an oral medication and has fewer gastrointestinal side effects than alendronate. Dosing options include 5 mg daily, 35 mg weekly, 75 mg twice monthly, and 150 mg monthly.

Ibandronate (Boniva)

Ibandronate has been shown to decrease the incidence of vertebral fractures by about 50%. However, it has not been shown to significantly reduce nonvertebral fractures. It is available oral or IV. The recommended dose is 150 mg every month by mouth or 3 mg IV every 3 months.

Zoledronic Acid (Reclast)

Zoledronic acid is the only exclusively IV preparation among the bisphosphonates. It has been shown to decrease vertebral fractures by 70%, hip fractures by 41%, and other nonvertebral fractures by 25% over 3 years in those with osteoporosis. Zoledronic acid is given as 5 mg IV once a year for osteoporosis treatment. For prevention in postmenopausal women, the same dose is given but every 2 years.

Hormonal

Hormone Replacement Therapy (HRT)

Hormone replacement therapy is FDA approved for the prevention of osteoporosis in women. However, it should not be used unless there are no viable alternatives due to safety issues. HRT has been shown to decrease vertebral and hip fractures by 34% but may increase risk of myocardial infarction, stroke, breast cancer, pulmonary embolus, and deep vein thrombosis [14]. These risks increase with higher doses and longer duration of use.

Estrogen Agonist/Antagonists

Estrogen Agonist/Antagonists work by acting on estrogen receptors within the bone to prevent resorption and have been shown to increase BMD and decrease vertebral fractures in postmenopausal women. However, they are less effective than bisphosphonates and carry a risk of venous thromboembolism similar to HRT. They may also cause menopausal symptoms during use. They are therefore considered second-line treatments. Raloxifine is the preferred agent in this category and has been shown to decrease the risk of breast cancer. It may be a reasonable alternative for postmenopausal women who cannot tolerate bisphosphonates or are at increased risk of invasive breast cancer. Premenopausal women should not be treated with estrogen agonist/antagonist as they may actually decrease BMD in this population [15].

Calcitonin

Calcitonin is an alternative treatment for osteoporosis. It inhibits bone resorption by binding to osteoclasts. It is available in several forms including

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intranasal, intramuscular, and subcutaneous. The nasal dosing is usually preferred due to ease of use and lower side effect profile. Though not as effective, calcitonin may be a reasonable alternative for patients unable to tolerate bisphosphonates [16]. It can also be used for short-term analgesia following a vertebral fracture [17].

Parathyroid Hormone (PTH)

PTH works as an anabolic agent by stimulating osteoblastic activity rather than reducing bone resorption. It is the only anabolic agent FDA approved for the prevention and treatment of osteoporosis. Two formulations are available, teriparatide (Forteo) and abaloparatide (Tymlos). It is administered in a daily subcutaneous injection and has been shown to significantly increase BMD and decrease fractures. PTH is not a first-line treatment because it can have more side effects than other agents. It can cause hypercalcemia, hyperuricemia, and increased risk of osteosarcoma, though this has not been confirmed in any human trials [18]. The FDA recommends limiting PTH therapy to 2 years until further longitudinal studies have been completed. The benefits of PTH fade quickly after discontinuation unless followed by antiresorptive therapy such as a bisphosphonate.

RANK Ligand Inhibitor

Denosumab (Prolia) is FDA approved for the treatment of osteoporosis in postmenopausal women with high risk of fracture. It has been shown to decrease vertebral and hip fractures at similar rates to bisphosphonates. It is given as subcutaneous injection every 6 months. It can decrease serum calcium levels, so any underlying hypocalcemia should be corrected prior to starting treatment [19]. Benefit fades quickly with discontinuation of denosumab and there may be an increased risk of multiple vertebral fractures. Because of this, patients should be counseled on the risks of missed doses and transitioned to an oral bisphosphonate after discontinuation.

Romosozumab (Evenity)

Romosozumab is FDA approved for the treatment of osteoporosis in women at high risk of fracture. It works by both anabolic and antiresorptive mechanisms. It is given as a subcutaneous injection of 210 mg each month for 12 months. After 1 year of treatment, patients must be transitioned to another antiresorptive therapy such as a bisphosphonate to maintain clinical benefits, much like PTH and denosumab. Romosozumab may increase the risk of serious cardiovascular events, limiting its use in those with high risk of such events, recent MI, or recent stroke. It is not currently recommended as a first line agent [4].

Monitoring and Duration of Treatment

DXA scans should not be repeated less than 2 years apart for most patients [7]. Optimal frequency of bone density monitoring is unknown, but evidence does not support routine monitoring with DXA every 2 years. For example, a study of women with normal or mildly osteopenic BMD found that 90% will remain in that range at 15 years. Only 10% will progress to osteoporosis [9]. Thus, intervals of up to 10–15 years may be appropriate for these patients. Among women with moderate or severe osteopenia, 10% developed osteoporosis at 5 years and 1 year, respectively [9]. DXA should be repeated when results will change management or rapid changes are expected [4].

For those on pharmacologic therapy, American College of Physicians (ACP) guidelines recommend against monitoring in the first five years of treatment based on evidence that treatment reduces fracture risk even in the absence of improvements in measured bone density [9]. Duration of treatment is commonly 5–10 years. It is reasonable to consider discontinuation after 5 years of treatment with an oral bisphosphonate. Patients at high risk of fracture may benefit from continuation beyond 5 years.

Conclusion

Osteoporosis is a common condition that greatly increases the risk of fracture with subsequent increases in morbidity and mortality. Measures should be taken early in life to prevent the development of osteoporosis including exercise,

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adequate calcium and vitamin D intake, and avoidance of tobacco and excessive alcohol use. A detailed history is essential to identify patients at increased risk of developing osteoporosis. Universal screening is recommended for all women at age 65 and above and should be considered in other patients at risk. DXA is the gold standard for screening and diagnosis of osteoporosis. Bisphosphonates are first-line therapy for both prevention and treatment of osteoporosis. The optimal interval for repeating DXA is unclear but up to 5 years for those being started on treatment with bisphosphonates and up to 10–15 years for those with normal or mildly low bone density may be appropriate. Patients with high risk of fracture may require monitoring as frequently as every 2 years. Routine monitoring with DXA every 1–2 years is likely unnecessary for most patients.

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Disorders of Nutrition

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Douglas J. Inciarte and Susan Evans

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Introduction

Nutrition disorders seen in primary care are common in the daily medical practice, either in the inpatient or outpatient setting. The assessment and management of nutritional disorders are linked to intestinal and liver disorders that interfere with the nutrient metabolism, affecting the overall care of the patient. Malabsorption of nutrients in the human body causes multiple symptoms and signs such as diarrhea, musculoskeletal, neurological, skin, and mucous membrane pathology resulting in weight loss, weakness, malnutrition, and electrolyte abnormalities.

This chapter will discuss the most common nutritional disorders by mineral or vitamin deficiency causing neurological disorders and other symptoms.

Vitamin and Mineral Deficiencies

Vitamin D Deficiency

Vitamin D deficiency continues to be fairly common in children and adults. In recent years, significant proportions of the populations in North America and global populations are affected with Vitamin D deficiency, although it is not consider

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as a pandemic. A consequence of low vitamin D levels resulted in rickets which was considered a disease that was essentially eliminated years ago after milk was fortified with vitamin D, we now know that even in utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities.

Applying the correct method to data from the National Health and Nutrition Examination Survey (NHANES) for 2007 through 2010 reveals that 13% of Americans 1 to 70 years of age are "at risk" for vitamin D inadequacy. Less than 6% are deficient in vitamin D [serum 25(OH)D levels <12.5 ng per milliliter.

Vitamin D deficiency in adults can increase the risk of osteopenia and osteoporosis and can cause osteomalacia and muscle weakness, thereby increasing the risk of fracture.

The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease [1].

Vitamin D is not a vitamin. It is a prohormone that is synthesized in the skin simplistic from a metabolite of cholesterol.

It is further metabolized to a family of molecules that principally function in the regulation of intestinal calcium absorption [2].

Solar ultraviolet B radiation (wavelength, 290–315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is rapidly converted to vitamin D3. Because any excess previtamin D3 or vitamin D3 is destroyed by sunlight, excessive exposure to sunlight does not cause vitamin D3 intoxication.

Few foods naturally contain or are fortified with vitamin D. Vitamin D2 is manufactured through ultraviolet irradiation of ergosterol from yeast and vitamin D3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used in over-the-counter vitamin D supplements, but the form available by prescription in the United States is vitamin D2. Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D, which is used to determine a patient's vitamin D status, and 25-hydroxyvitamin D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1α- hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D. The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels. The efficiency of the absorption of renal calcium and of intestinal calcium and phosphorus is increased in the presence of 1,25-dihydroxyvitamin D [1].

Patients with chronic kidney disease (CKD) are at a higher risk of vitamin D deficiency due to either renal losses or decreased synthesis of 1,25-dihydroxyvitamin D. Measuring parathyroid hormone (PTH) levels to identify optimal levels of Vitamin D 25(OH) remains controversial as the relationship between both is inconsistent.

Because vitamin D is produced by the actions of sunlight on the skin, its deficiency does not usually represent a dietary deficiency, but is seen in those whose skin exposure to ultraviolet light is inadequate; this group includes individuals who, as a result of illness or frailty, seldom venture outdoors, who live at high latitude (particularly if they have dark skin), and who habitually completely cover their skin (e.g., veiled women). The melanin in pigmented skin absorbs ultraviolet light and reduces vitamin D synthesis. This is a valuable protective mechanism in those living in intensely sunny climates, but becomes a liability when these individuals move to relatively sunless environments, such as the cities of Northern Europe and North America. Low 25-hydroxyvitamin D levels are found in the exclusively breastfed infants of vitamin D-deficient mothers, so supplementation of pregnant women and their infants in high-risk groups is advised [3].

Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter) [4–6].

Serum 25-hydroxyvitamin D level is the best indicator to assess overall vitamin D levels due to that this measurement reflects total vitamin D from dietary intake and sunlight exposure, as

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well as the conversion of vitamin D from adipose stores in the liver.

Symptoms of vitamin D deficiency are related to rickets in children and osteomalacia in adults. It is very common that patients with vitamin D deficiency can present with bone pain, fatigue fractures, muscular cramps, muscle pain, and gait disorders, with an increased incidence of falls in the elderly [7].

Vitamin D deficiency is treated with vitamin D oral supplementation, and the recommended dose of vitamin D depends upon the nature and severity of the vitamin D deficiency.

In patients who do not have problems absorbing vitamin D:

- If 25-hydroxyvitamin (25-OH-D) is less than 20 ng/mL (50 nmol/L), treatment includes 50,000 international units of vitamin D2 or D3 by mouth once per week for 6–8 weeks, and then 800–1,000 (or more) international units of vitamin D3 daily thereafter. The vitamin D levels should be retested in 6 weeks after the treatment was started.
- In patients with a level between 20 and 30 ng/mL (50–75 nmol/L), treatment usually includes 800–1,000 international units of vitamin D3 by mouth daily, usually for a 3-month period. However, many individuals will need higher doses.
- Once a normal level is achieved, continued therapy with 800 international units of vitamin D per day is usually recommended.
- In infants and children whose 25-OH-D is less than 20 ng/mL (50 nmol/L), treatment usually includes 1,000–5,000 international units of vitamin D2 by mouth per day (depending on the age of the child) for 2–3 months.
- In patients who have diseases or conditions that prevent them from absorbing vitamin D normally (e.g., kidney or liver disease), the recommended dose of vitamin D will be determined on an individual basis. When vitamin D level is normal (>30 ng/mL [≥75 nmol/L]), a dose of 800 international units of vitamin D per day is usually recommended [8].
- Vitamin D dosing represents the safe boundary at the high end of the scale and should not be misunderstood as amounts people need or should strive to consume. While these values vary somewhat by age, intakes of vitamin D should not surpass 4,000 IUs per day, due to increased risk for harm. Once intakes surpass 2,000 IU per day for calcium, the risk for harm also increases. As Americans take more supplements and eat more of foods that have been fortified with vitamin D and calcium, it becomes more likely that people consume high amounts of these nutrients. Kidney stones have been associated with taking too much calcium from dietary supplements. Very high levels of vitamin D (above 10,000 IUs per day) are known to cause kidney and tissue damage [9].

Vitamin B12 Deficiency

Vitamin B_{12} (cobalamin) deficiency was recognized as a health concern nearly 100 years ago and continues to have clinical significance.

It is particularly common in the elderly (>65 years of age), but is often unrecognized because of its subtle clinical manifestations, although they can be potentially serious, particularly from a neuropsychiatric and hematological perspective. In the general population, the main causes of cobalamin deficiency are pernicious anemia and food-cobalamin malabsorption.

Food-cobalamin malabsorption syndrome, which has only recently been identified, is a disorder characterized by the inability to release cobalamin from food or its binding proteins.

Cobalamin malabsorption syndrome is usually caused by atrophic gastritis, related or unrelated to *Helicobacter pylori* infection, and long-term ingestion of antacids and biguanides [10].

Both the clinical recognition of vitamin B12 deficiency and confirmation of the diagnosis by means of testing can be difficult. The patient's history may include symptoms of anemia, underlying disorders causing malabsorption, and neurologic symptoms.

The most common neurologic symptoms are symmetric paresthesia or numbness and gait problems [11, 12].

Physical examination may reveal pallor, edema, pigmentary disorders in the skin, jaundice, or neurologic defects such as impaired vibration

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sense, impaired position and cutaneous sensation, ataxia, and general weakness.

The first test performed to confirm the diagnosis of vitamin B12 deficiency is generally measurement of the serum vitamin B12 level. Both false negative and false positive values are common (occurring in up to 50% of tests) with the use of the laboratory-reported lower limit of the normal range as a cutoff point for deficiency [11].

Given the limitations of available assays, clinicians should not use a laboratory's reported lower limit of the normal range to rule out the diagnosis of vitamin B12 deficiency in patients with compatible clinical abnormalities; because of this concern, obtaining a methylmalonic acid (MMA) level, total homocysteine, or both is useful in making the diagnosis of vitamin B12 deficiency in patients who have not received treatment. The levels of both methylmalonic acid and total homocysteine are markedly elevated in the vast majority (>98%) of patients with clinical B12 deficiency [13].

Elevated levels of MMA and total homocysteine decrease immediately after treatment, and the levels can be remeasured to document adequate vitamin B12 replacement.

The level of serum total homocysteine is less specific, since it is also elevated in folate deficiency [13], classic homocystinuria, and renal failure.

If the patient consumes sufficient amounts of vitamin B12 and has clinically confirmed B12 deficiency, then malabsorption (pernicious anemia) must be present. Chronic atrophic gastritis and intestinal vitamin B12 malabsorption should be investigated. A positive test for anti-intrinsic factor or antiparietal cell (both highly specific 100% and 50–100%) antibodies is indicative of pernicious anemia; surveillance for autoimmune thyroid disease is reasonable in patients with positive antibody tests.

Chronic atrophic gastritis can be diagnosed on the basis of an elevated fasting serum gastrin level and a low level of serum pepsinogen I [14]. Some experts recommend endoscopy to confirm gastritis and rule out gastric carcinoid and other gastric cancers, since patients with pernicious anemia are at increased risk for such cancers [14].

For the treatment of vitamin B12 deficiency, oral replacement must be considered. Healthy older adults should consider taking supplemental crystalline vitamin B12 as recommended by the Food and Nutrition Board. Unfortunately, most patients with clinical vitamin B12 deficiency have malabsorption and will require parenteral or high-dose oral replacement. Adequate supplementation results in resolution of megaloblastic anemia and resolution of or improvement in myelopathy.

The most recommended treatment is schedules for injections of vitamin B12 (called cyanocobalamin in the United States and hydroxocobalamin in Europe) [15, 16].

Patients with severe disease should receive injections of 1,000 μg at least several times per week for 1–2 weeks, then weekly until clear improvement is shown, followed by monthly injections. Hematologic response is rapid, with an increase in the reticulocyte count in 1 week and correction of megaloblastic anemia in 6–8 weeks. Patients with severe anemia and cardiac symptoms should be treated with transfusion and diuretic agents, and electrolytes should be monitored. Neurologic symptoms may worsen transiently and then subside over weeks to months [12].

The treatment for pernicious anemia is lifelong, and in patients in whom vitamin B12 supplementation is discontinued after clinical recovery, past neurologic symptoms will recur within as short a period as 6 months, and megaloblastic anemia recurs in several years [15].

Folic Acid Deficiency

Folic acid or folate refers to a family of compounds that belongs to the group of vitamin B cofactors that participate in the methylation of homocysteine to methionine and to the conversion of S-adenosylmethionine (SAM), the universal methyl donor, to processes involving DNA, RNA, hormones, neurotransmitters, membrane lipids, and proteins. Food folates are present in animal products as well as green leafy vegetables, fruits, cereals and grains, nuts, and meats.

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The most common cause of folic acid or folate deficiency is nutritional, either due to poor diet and/or alcoholism. Normal body stores are small (5–10 mg), and individuals on a folate-deficient diet and/or alcoholics can develop megaloblastic anemia within 4–5 months, even sooner if they have a low folate intake (5–10 weeks) [17].

In child-bearing women, a high dose of folic acid supplement reduces the incidence of recurrent neural tube defects by 70% [18].

Folate deficiency is also common in elderly older adults. In one study the age-specific prevalence of folate deficiency was approximately 5–10% in those ages 65–74 years [19].

Alcohol abuse produces a sharp fall in serum folate within 2–4 days by impairing its enterohepatic cycle and inhibiting its absorption. Alcoholics can develop megaloblastosis within 5–10 weeks. Folate depletion is quicker than the 4–5 months required in normal patients in part because alcoholics often have lower folate stores due to previous dietary habits.

Several drugs interfere with folic acid metabolism including trimethoprim, pyrimethamine, methotrexate, and phenytoin.

The classic clinical presentation of folate deficiency is quite different from that of B12 deficiency; in folic acid deficiency, it is rare to see neurological changes or symptoms.

Exceptions to this general rule are the rare cases of hereditary folate malabsorption and/or metabolism, which are associated with progressive neurologic deterioration early in life [20]. For the diagnosis of folate deficiency, one must obtain assays of serum or red cell folate, serum B12, methylmalonate, and homocysteine to distinguish between folate and vitamin B12 deficiency.

The treatment of folic acid deficiency is 1–5 mg per day of oral folate supplementation, and the duration of the treatment should be for 1–4 months or until complete hematologic recovery occurs.

A dose of 1 mg per day of folic acid is usually sufficient and recommended for disease prevention in normal adults, alcoholics, the elderly, and prevention of neural tube defects in female patients of child-bearing age.

Iron Deficiency

Iron deficiency is the most prevalent nutritional deficiency worldwide affecting people in both developing and developed countries. Globally, iron deficiency anemia caused 34.7 million years lived with disability between 2000 and 2016 which puts in in the top five causes of disability globally (GDB 2016) [21]. Iron deficiency is prevalent in pediatric patients and in premenopausal women in both low-income and developed countries [21].

Symptoms of iron deficiency can include pallor, fatigue, cheilosis, and atrophy of the lingual papillae. In developing countries, the most common causes of iron deficiency are poor dietary intake and chronic blood loss due to parasitic infections. In developed countries, those at risk include children up to age 5 due to their rapid growth and menstruating and pregnant women. Gastrointestinal conditions resulting in malabsorption, a history of weight loss surgery, gastrointestinal bleed, gastrointestinal cancer, or the use of antiacid medicines can cause iron deficiency. The elderly are also at risk due to increased prevalence of chronic disease and medication use such as aspirin, NSAIDs, and anticoagulants. (Lopez) [22].

While a low hemoglobin level diagnoses anemia, it is not a good screening test for iron deficiency because many people are iron deficient while their hemoglobin remains normal. A low ferritin <15 μg is diagnostic of iron deficiency, but a normal ferritin does not rule out iron deficiency in the context of inflammation. A higher cutoff for ferritin such as 30 μg has been recommended to increase the sensitivity of ferritin for iron deficiency. In iron deficiency, serum iron will be reduced and total iron-binding capacity will be increased. This results in a decrease in transferrin saturation to less than 16% or less than 20% in the context of inflammation. (Lopez) [22].

Iron replacement therapy can be administered orally or parenterally. The recommended dose for adults is 100–200 mg elemental iron in divided daily doses taken without food. Children are recommended to take 3–6 mg per kg body weight of liquid iron daily. While this should lead to rapid

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improvement, ongoing therapy for several months may be needed to replete iron stores. Long-term use of oral iron is limited by side effects including nausea, vomiting, constipation, and metallic taste. Parenteral replacement of iron has become more common with newer and safer intravenous iron and is indicated when blood loss is too rapid for oral replacement, the patient is not able to absorb oral iron or is unable to tolerate the side effects. The dose of iron needed is calculated with the following formula: body weight in kg × 2.3 × hemoglobin deficiency. Hemoglobin deficiency is the target hemoglobin level – patient hemoglobin level. Another 500–1000 mg iron can be added to replace iron stores. There are several forms of IV iron available in the USA including iron sucrose which is often given at a dose of 200 mg IV over 2–5 min and repeated until the target dose is reached. (Camaschella) [23].

Malnutrition

Malnutrition is a very important problem that is encountered more often than expected in medical practice and results from inadequate or poor-quality food intake or from diseases that alter food intake or nutrient requirements, metabolism, or absorption.

Malnutrition can be classified via primary and secondary causes. Primary malnutrition presents in third-world or developing countries where social or political conditions have deteriorated. Secondary malnutrition is seen in first-world or industrialized countries. It presents in populations with adequate food supplies which can become malnourished as a result of acute or chronic diseases that alter nutrient intake or metabolism, particularly diseases that cause acute or chronic inflammation.

In terms of primary malnutrition, the most common diseases are *marasmus* and *kwashiorkor*. Marasmus results from long-term deficit of dietary energy. Kwashiorkor is the result of a poor protein intake diet. Energy-poor diets with minimal inflammation cause gradual erosion of body mass, resulting in classic marasmus. By contrast, inflammation from acute illnesses such as injury or sepsis or from chronic illnesses such as cancer, lung or heart disease, or HIV infection can erode lean body mass even in the presence of relatively sufficient dietary intake, leading to a kwashiorkor-like state. Quite often, inflammatory illnesses impair appetite and dietary intake, producing combinations of the two conditions [24].

The difference between marasmus and cachexia is that marasmus is a starvation-related malnutrition where all available body fat stores have been exhausted due to starvation without systemic inflammation. Cachexia is related to chronic disease malnutrition with loss of lean body mass due to chronic systemic inflammation. The diagnosis is based on fat and muscle wastage resulting from prolonged calorie deficiency and/or inflammation. Diminished skinfold thickness reflects the loss of fat reserves; reduced arm muscle circumference with temporal and interosseous muscle wasting reflects the catabolism of protein throughout the body, including in vital organs such as the heart, liver, and kidneys [24].

Routine laboratory findings in cachexia/marasmus are relatively unremarkable. The creatinine-height index (24-h urinary creatinine excretion compared with normal values based on height) is low, reflecting the loss of muscle mass. Occasionally, the serum albumin level is reduced, but it remains above 2.8 g/dL when systemic inflammation is absent. In kwashiorkor there is a connection with acute, life-threatening conditions such as trauma and sepsis. The physiologic stress produced by these illnesses increases protein and energy requirements at a time when intake is often limited. Physical exam and laboratory findings include increased hair pluckability, edema, skin breakdown, and poor wound healing with severe decrease of albumin (<2.8 g/dL) and transferrin (<150 mg/dL). Lymphocytopenia (<1,500 lymphocytes/μL) can be also encountered.

Other mineral deficiencies such as vitamin C and zinc are relatively common in sick patients. Scurvy is rare in developed countries. Signs of corkscrew hairs on the lower extremities are found frequently in chronically ill and/or alcoholic patients. Scurvy can be diagnosed by determination of plasma vitamin C levels. Low zinc levels are common in patients with malabsorption

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syndromes such as inflammatory bowel disease, and they present with poor wound healing, pressure ulcer formation, and impaired immunity.

Thiamine deficiency is a common problem of alcoholism and is replaced with oral formulations.

The treatment of vitamin C deficiency is 250–500 mg/d of oral formulations. Patients with zinc deficiencies will need oral supplementation with 220 mg of zinc sulfate one to three times daily.

In the inpatient setting, hypophosphatemia results from rapid intracellular shifts of phosphate in underweight or alcoholic patients receiving intravenous glucose, with numerous complications such as acute cardiopulmonary failure, collectively called refeeding syndrome, and can be life-threatening; in these situations, consulting a clinical nutritionist is necessary.

Nutritional Requirements for Health Maintenance, Gender/Age/Disease, or Activity

Data from the 2007 to 2008 National Health and Nutrition Examination Survey (NHANES) suggested that nearly half of US adults aged 20–69 reported taking at least one dietary supplement in the past month. The factors that were independently associated with a greater likelihood of supplement use are as follows: being female, older, white race, having higher level of education, nonsupplemental nutrition access program (SNAP) participation, and living in a food-secure household. When considering nutrients from food, supplement users tended to consume greater amounts of vitamin A, vitamin C, vitamin E, folic acid, calcium, and iron. There was no association between supplement use and daily intakes of vitamin B12 and zinc from food sources only. Including nutrients from daily supplement use, supplement users consumed greater amounts of all eight nutrients [25].

One research study regarding the use of vitamins did show additional support for the conclusion that the vast majority of consumers recognize that multivitamins and other supplements can be helpful in filling nutrient gaps in the diet but should not be viewed as replacements for a healthy diet or healthy lifestyle habits. This finding suggests that policy makers and health professionals could feel comfortable recommending rational dietary supplementation as one means of improving nutrient intakes, without being unduly concerned that such a recommendation would lead consumers to discount the importance of good dietary habits.

The online tool at http://fnic.nal.usda.gov/interactiveDRI/ allows health professionals to calculate individualized daily nutrient recommendations for dietary planning based on the DRIs for persons of a given age, sex, and weight. To provide guidance for food education, a good reference is the U.S. Department of Agriculture (USDA) MyPlate Food Guide for individuals (www.supertracker.usda.gov/default.aspx), to create food-exchange lists for therapeutic diet planning, and as a standard for describing the nutritional content of foods and nutrient-containing dietary supplements [26].

The authors conclude that a well-balanced lifestyle along with exercise should never be replaced by the use of vitamins; however, the use of daily calcium, vitamin D, and folic acid in child-bearing women has been proven to prevent diseases.

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Selected Disorders of the Endocrine and Metabolic System

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The endocrine system governs the metabolic activities of the body, affects tissue growth, and regulates the functioning of many organ systems that influence behavior and cognition. Because the endocrine system is involved in an extraordinary range of physiological processes, it is important to consider an endocrine disorder in many clinical situations, especially when a patient presents with vague multisystem complaints.

The Pituitary

The pituitary is often called the master gland as it controls most of the other endocrine glands' function. The hypothalamus regulates most of the pituitary gland's hormone secretion in response to target gland stimulation requirements. The pituitary has two functional parts the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The pituitary also has a vestigial intermediate lobe. The hypothalamus secretes oxytocin and vasopressin (also known as arginine vasopressin, antidiuretic hormone [ADH], and argipressin) through the posterior pituitary. The hypothalamus secretes regulatory hormones (e.g., gonadotropin-releasing hormone [GnRH]) which control the secretion of anterior pituitary hormones in a pulsatile pattern every 1–3 h. The anterior pituitary secretes six main hormones which are the following: growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (see Table 1 for more details). Pituitary gland disorders usually originate from adenomas that either overproduce hormones

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Table 1 Hormones of the anterior pituitary

Pituitary cell type (staining characteristic)	Hormones secreted	Target site	Clinical excess	Clinical deficiency
Somatotrophs (eosinophilic)	GH	Bones	Gigantism; acromegaly	Dwarfism
		Glucose metabolism	Glucose intolerance	Fasting hypoglycemia
Lactotrophs (eosinophilic)	Prolactin	Breasts	Galactorrhea	Inability to lactate
Corticotrophs (basophilic)	ACTH	Adrenal cortex	Cushing's syndrome	Adrenal insufficiency
	B-Lipoprotein	Skin	Hyperpigmentation	Hypopigmentation
Thyrotrophs (chromophobic)	TSH	Thyroid	Hyperthyroidism	Hypothyroidism
Gonadotrophs (chromophobic)	FSH, LH	Females: ovaries Males: testes	Precocious puberty	Delayed puberty; infertility; loss of secondary sexual characteristics

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid stimulating hormone

or cause underproduction by obstructing portal veins. Hormone-secreting adenomas usually produce a single hormone which is typically prolactin, GH, or ACTH.

Hyperprolactinemia and Galactorrhea

Overview

Prolactin is synthesized and secreted by the anterior lobe of the pituitary gland [1]. Its two main functions are the development of mammary glands within breast tissue and milk production. It also maintains lactation of the primed breast. The hypothalamus secretes dopamine which inhibits prolactin release, and thyrotropin-releasing hormone (TRH) stimulates prolactin release. Estrogen, epidermal growth factor, and dopamine receptor antagonists also induce prolactin release.

Hyperprolactinemia can develop from pituitary tumors, pharmacotherapy, external stimulation, or pathological interruption of the hypothalamic-pituitary dopaminergic pathways (see Table 2 for a more complete list). Chronic conditions such as renal failure, cirrhosis, and hypothyroidism can also cause hyperprolactinemia. Hyperprolactinemia may be asymptomatic or result in hypogonadism, infertility, galactorrhea, and bone loss. Decrease in bone density from hyperprolactinemia occurs secondary to sex steroid attenuation. The population prevalence of prolactinomas peaks between ages 25 and 34 years with an estimated prevalence between 6 and 50 cases per 100,000 [2, 3].

Clinical Presentation

Women with hyperprolactinemia typically present with symptoms ranging from shortened luteal phases, vaginal dryness, infertility, decreased libido, and oligomenorrhea to hypogonadism, galactorrhea, amenorrhea, and osteopenia [1, 4]. Higher levels of prolactin are associated with worsening symptoms. Men can present with decreased libido, impotence, decreased sperm production, infertility, gynecomastia, erectile dysfunction, and rarely galactorrhea. Patients with macroadenomas may also present with headaches or changes in vision.

Diagnosis

The diagnosis of hyperprolactinemia is generally confirmed with a single measurement of serum

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Table 2 Selected causes of hypopituitarism [7]

Neoplastic	**Pharmacologic**
Pituitary adenoma	Anesthetics
Craniopharyngioma	Anticonvulsants
Meningioma	Antidepressants
Cysts (Rathke's cleft, arachnoid, epidermoid, dermoid)	Antihistamines
Germinoma	Antihypertensives
Glioma	Cholinergic agonists
Astrocytoma	Drug-induced hypersecretion
Ganglioneuroma	Catecholamine depletory
Paraganglioma	Dopamine receptor blockers
Teratoma	Dopamine synthesis inhibitors
Chordoma	Estrogen
Pituicytoma	Neuroleptics/antipsychotics
Ependymoma	Neuropeptides
Pituitary carcinoma	Opiates and opiate antagonists
Metastases	
Treatment of sellar, parasellar, and hypothalamic disease	**Traumatic**
Surgery	Head injury
Radiotherapy	
Infectious	**Vascular**
Bacterial	Pituitary tumor apoplexy
Fungal	Sheehan's syndrome
Parasites	Intrasellar carotid artery aneurysm
Tuberculosis	Subarachnoid hemorrhage
Syphilis	
Infiltrative/inflammatory disease	**Miscellaneous causes**
Autoimmune disease	Pituitary apoplexy
Hemochromatosis	Cavernous sinus thrombosis
Granulomatous	Primary empty sella syndrome
Langerhans cell histiocytosis	Immunologic
Giant cell granuloma	Idiopathic
Xanthomatous hypophysitis	

prolactin above the upper limit of normal (25 mcg/L); however, morning prolactin levels (4 to 6 a.m.) can peak to 30 mcg/L [4]. Borderline elevated values can be confirmed by measuring prolactin levels every 15 to 20 min to identify possible prolactin pulsatility [1]. Marked serum prolactin levels >100 mcg/L are associated with hypogonadism, galactorrhea, and amenorrhea. Osteopenia presents mainly with hypogonadism. Serum prolactin levels between 51 and 75 mcg/L are associated with oligomenorrhea. Mild prolactin excess with levels between 31 and 50 mcg/L is associated with short luteal phases and decreased libido. Men typically present with decreased libido, impotence, decreased sperm production, infertility, and rarely gynecomastia and galactorrhea. Serum prolactin levels above 200 mcg/L indicate the presence of a lactotroph adenoma.

Diagnosis of suspected drug-induced symptomatic hyperprolactinemia involves discontinuation of the offending agent followed by measurement of serum prolactin 3 days later [1]. An alternative medication should be used if possible and antipsychotic agents should be substituted or discontinued cautiously. A pituitary MRI can identify pituitary or hypothalamic masses if the offending agent cannot be discontinued. Additionally, visual field testing can identify macroadenomas along with aid from pituitary MRI.

Management

The management of hyperprolactinemia changes depending on the etiology [1]. Drug-induced

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hypogonadism treatment involves discontinuation of the offending agent if possible. An alternative medication not known to cause hyperprolactinemia should be used instead. If substitution is not possible, a dopamine agonist can cautiously be used to attenuate hyperprolactinemia symptoms. Dopamine agonists are also used in the treatment of symptomatic prolactinomas (both micro- and macroadenomas) to lower serum prolactin, decrease tumor size, and restore gonadal function.

Cabergoline is the first-line dopamine agonist as it normalizes prolactin levels and shrinks pituitary tumors more effectively than bromocriptine. The initial cabergoline dose is 0.25 mg twice weekly and can be titrated up to 1 mg twice weekly (every 4 weeks) to normalize prolactin levels. Cabergoline use is associated with valvular regurgitation, and high doses should be used cautiously [5]. Bromocriptine, a dopamine agonist, may be used second line and can be administered intravaginally if patients are intolerant to oral administration [1]. Dopamine agonists may be tapered and discontinued after 2 years minimum treatment if serum prolactin has normalized and previous tumors are no longer visible on MRI.

Patients with amenorrhea secondary to microadenomas can be treated with either dopamine agonists or oral contraceptives [1]. Patients that develop long-term hypogonadism or low bone mass should be treated with estrogen or testosterone. Asymptomatic patients should not be treated. Transsphenoidal surgery in patients with prolactinomas is considered if patients either cannot tolerate high doses of cabergoline or are unresponsive to dopamine therapy. Radiation is an alternative if surgery fails or in situations with malignant prolactinomas.

Hypopituitarism

Overview

Hypofunction of the pituitary presents as either partial or complete (panhypopituitarism) reduction in pituitary hormones. It is a rare disorder with an estimated prevalence of 45 cases per 100,000 [6]. The disorder includes adrenal insufficiency, hypothyroidism, hypogonadism, GH deficiency, and diabetes insipidus (DI) [7]. Causes of hypopituitarism are varied and include both disturbances of the gland directly (primary hypopituitarism) or the hypothalamus (secondary hypopituitarism) (see Table 2).

Clinical Presentation

Hypopituitarism typically presents as progressive hormone deficiencies starting with GH followed by gonadotropins, TSH, and ACTH [7]. However, exceptions exist to the order which makes identifying a specific hormone deficiency challenging as partial function loss may mimic primary failure of the target site. Symptoms may develop abruptly (as in Sheehan's syndrome) or slowly (as with a slow-growing nonsecretory adenoma). Children may present with growth failure and delayed puberty. Adults typically present with a confusing array of psychological problems, family or social difficulties, and multisystem somatic complaints that are due to hormonal deficiencies and the underlying disease that causes the hypopituitarism. Common complaints include fatigue, weight loss, dry skin, menstrual abnormalities, and sexual dysfunction; however, a wide range of manifestations are possible [7].

Panhypopituitarism is ultimately fatal. Patients appear pale and chronically ill with a loss of secondary sexual characteristics. Galactorrhea can occur in secondary hypopituitarism (e.g., hypothalamic sarcoidosis) because the hypothalamus inhibits pituitary prolactin. Lack of vasopressin produces polydipsia and polyuria of central DI.

Diagnosis

The diagnosis of hypopituitarism begins with a full clinical history and physical examination [7]. Hypopituitarism manifests as reduction in target gland hormone levels such as GH, prolactin, ACTH, TSH, LH, and FSH. Reduction in vasopressin may occur if the posterior pituitary

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is affected. Obtaining a hormonal assay and knowing the characteristics and limitations are essential when confirming the diagnosis.

Management

Treatment involves the hormonal replacement of panhypopituitarism [7]. A specialist consult should be obtained to oversee treatment as target gland hormonal replacement should attempt to mimic normal physiologic patterns. A deficiency of glucocorticoids is corrected before thyroid hormone replacement to prevent precipitating an adrenal crisis. Because aldosterone secretion is unaffected, mineralocorticoids are not necessary. Sex hormones can be started once the patient is euthyroid, but gonadotropins are required to restore fertility. In children, GH is required. In adults, replacement of GH reduces body fat, increases muscle mass and bone density, and improves exercise tolerance in the short term; the long-term benefits have not been evaluated. At least one study has suggested that patients affected by traumatic brain injury may demonstrate a higher percentage of abnormality in GH production, which may improve after 1 year [8]. Patients with hypopituitarism should wear a medical identification bracelet or necklace.

Neuroendocrine Disorders of Water Balance

Endocrine diseases may manifest as disorders of water balance such as hypernatremia, hyponatremia, polydipsia, or polyuria. Osmotic homeostasis is regulated by a complex coordination between the endocrine system, brain, heart, and kidneys. Plasma tonicity and blood volume are the two factors that affect this homeostasis. Blood volume is detected by baroreceptors and the pressure exerted on the renal blood vessels. The plasma tonicity is monitored by the hypothalamus' osmoreceptors; when there is hypernatremia, the thirst mechanism and the release of ADH are concurrently stimulated.

Polydipsia

Primary Polydipsia

Primary polydipsia (PP) means excessive fluid intake that is not secondary to deficient ADH production or response. Excessive volume expansion can cause hyponatremia and inhibit ADH release. A central defect in thirst regulation is presumed to play a significant role in primary polydipsia, but the mechanism is still unknown; the disorder itself is known as dipsogenic DI. PP can be induced by hypothalamic lesions, caused by infiltrative diseases like sarcoidosis, that affect the thirst center. It is important to perform a cranial MRI to observe the hypothalamus before idiopathic or psychogenic polydipsia is presumed. An iatrogenic source should also be considered as certain drugs (e.g., anticholinergics) can cause dry mouth. PP can also be seen in anxious patients preparing for imaging or attempting to dilute their urine to avoid a positive urine drug screening [9].

Secondary Polydipsia

Secondary polydipsia is a protective measure against polyuria of any etiology. Dehydration can otherwise result in hypernatremia and possible death. For psychiatric patients with polyuria or hyponatremia, it should not be automatically assumed that psychogenic polydipsia is the cause. A water deprivation test can be helpful in evaluating for central or nephrogenic DI versus PP. The clinician should use imaging and lab values to assess for hypopituitarism. Assessment of thyroid, adrenal, and renal function can help rule out other causes.

Polyuria and Central Diabetes Insipidus

Polyuria can be due to osmotic (solute) diuresis or water diuresis. Osmotic diuresis includes glucosuria, urea diuresis, administration of high amounts of protein orally (or via IV or feeding tube), mannitol diuresis, and sodium diuresis (e.g., large volumes of IV saline or after resolution

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of bilateral urinary tract obstruction). Common causes of glucosuria are uncontrolled diabetes mellitus, excess IV dextrose and water, or administration of sodium-glucose transport 2 inhibitors. Examples of urea diuresis include acute kidney injury and tissue catabolism (which can be secondary to glucocorticoid therapy). Water diuresis includes PP (seen mainly in adults and adolescents), nephrogenic DI, and central DI. Central DI is due to ADH deficiency which can be caused by destruction of the posterior pituitary's capillary beds or loss of the hypothalamic neurons that produce vasopressin [10]. Acquired central DI generally is caused by head trauma or transsphenoidal surgery. Central DI can be complete or partial, permanent or temporary, and the solely presenting condition or associated with other pituitary abnormalities. It can be inherited as an X-linked or autosomal dominant disease. Pregnancy can produce transient central DI.

Clinical Presentation

Polyuria and polydipsia are the main findings in idiopathic central DI [10]. Acquired central DI may additionally present with associated pituitary lesion symptoms. The onset of central DI may be abrupt or gradual depending on the etiology. Patients with central DI present with polyuria (>3 L/day in adults and >2 L/m^2 in children) that should be differentiated from urinary frequency and nocturia. A dilute urine osmolality <300 mosmol/kg suggests nephrogenic or complete central DI, but a urine osmolality between 300 and 600 mosmol/kg indicates osmotic diuresis, PP, or partial central DI. Nocturia may be present in either case.

Diagnosis

A two-step water restriction test is commonly used to diagnose different types of DI [10]. The test is performed over 8 h. It is designed to dehydrate the patient, causing stimulation ADH which should concentrate urine osmolality. During the test weight and sodium osmolarity of the plasma and urine are measured hourly. At the conclusion of the test, a urine concentration >750 mosmol/kg is normal, whereas a concentration <300 mosmol/kg indicates either central or nephrogenic DI. Desmopressin is administered after the dehydration test; if the urine concentrates to >750 mosmol/kg, the patient likely has central DI, and if the urine fails to concentrate, that indicates nephrogenic DI. The water restriction test should be performed by a specialist as there are safety concerns associated with the test.

Copeptin assays are a developing diagnostic tool for DI. Copeptin is the C-terminal locus of the vasopressin prohormone, prepro-vasopressin, and a surrogate marker for endogenous ADH. It is easier to monitor than serum ADH and has a high diagnostic specificity [11]. Distinction between central DI and primary polydipsia can also be aided by T1-weighted MRI studies of the posterior pituitary and hypothalamus [10].

Management

Treatment of central DI requires identification and treatment of the underlying cause [10]. Treatment includes replacement of free water deficit and replacement of ADH. Desmopressin acetate given intranasally is the first-line treatment for ADH-deficient DI. Desmopressin nasal may cause rhinitis or conjunctivitis, so oral desmopressin may be considered instead. Oral desmopressin is initiated at 0.05 mg twice daily and, if needed, increased to a maximum of 0.4 mg every 8 h. With the oral route, gastrointestinal symptoms, asthenia, and mild elevation in hepatic enzymes may occur. Other therapeutic agents for central DI are hydrochlorothiazide, clofibrate, and ADH-releasing drugs (e.g., carbamazepine, chlorpropamide). The patient should also wear a medical alert bracelet.

Disorders of Secondary Sexual Characteristics

Secondary sexual characteristics are initially expressed at puberty and are maintained in adults by the sex hormones.

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Normal Puberty

The cognitive, physical, and psychological transformation that occurs during adolescence is referred to as puberty. It occurs in two unique stages known as adrenarche and gonadarche. The results of normal puberty are most notable for the development of secondary sexual characteristics. Adrenarche results from increased production of androgens by the adrenal cortex. This normally occurs between the ages of 6 and 8. Physical manifestations of adrenarche include skeletal bone growth and further development of the pilosebaceous units and apocrine sweat glands. Gonadarche is driven by the hypothalamic-pituitary-gonadal axis. Increased pulsatile release of GnRH from the hypothalamus stimulates pulsatile secretion of FSH and LH from the pituitary gland. These hormonal pulsations have different impacts on the development of boys and girls, respectively.

In girls, FSH stimulates development of the ovarian follicles and granulosa cells, whereas LH stimulates ovarian theca cells. Together this leads to the production of estrogens, primarily estradiol. Estradiol is responsible for breast development (thelarche), growth acceleration, and skeletal maturation. The developing ovarian follicles eventually results in ovulation and development of the corpus luteum. Progesterone produced by the corpus luteum along with the effects of estradiol leads to menstruation (menarche). The median age at menarche in the USA decreased from 12.1 in 1995 to 11.9 in 2013–2017 [12]. This is thought to be secondary to the rising rates of childhood obesity as a higher body mass index correlates with an earlier onset of puberty [13].

In boys, LH stimulates the production of testosterone by the Leydig cells of the testes. Testosterone has multiple impacts including development of the seminiferous tubules and spermarche. Testosterone also drives increases in muscular mass, growth of the penis, and deepening of the voice. The impact of FSH is seen through the development of spermatozoa and enlargement of the testes.

Precocious Puberty

Precocious puberty is defined as the development of secondary sexual characteristics prior to the age of 8 years in girls and 9 years in boys [14]. This age distribution is 2–2.5 standard deviations from the norm which is considered 10.5 years of age in girls and 11.5 years of age in boys. Precocious puberty is caused by central or peripheral factors as seen below:

- Central precocious puberty
  - True precocious puberty
  - Central nervous system lesions
  - Gonadotropin-secreting tumor
  - Profound hypothyroidism
  - Chronic adrenal insufficiency
- Peripheral (pseudo) precocious puberty
  - Ovarian tumor
  - Follicular cysts
  - Exogenous estrogens
  - Testicular tumor
  - Autonomous Leydig cell formation
  - Exogenous androgens
  - Polyostotic fibrous dysplasia
  - Adrenal tumor
  - Adrenal hyperplasia

Central precocious puberty is driven by early activation of the hypothalamic-pituitary-gonadal axis resulting in the early production of gonadotropins. It can be separated from peripheral causes in that while pubertal development is early, it progresses in the normal sequence of development. Central precocious puberty is more common in girls, and most cases, especially in girls, are idiopathic. If central precocious puberty begins before the age of 6, a pathologic process such as a CNS tumor is more likely. As central precocious puberty is driven by GnRH, long-acting analogs of GnRH are the mainstay of treatment [15]. For many years, the most common treatment in the United States was monthly intramuscular (IM) depot leuprolide. During the past decades, there has been a substantial increase in the number of extended-release formulations of GnRH agonists including 3- and 6-month IM

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depot preparations and a subcutaneous implant that is marketed for annual use [16].

Peripheral precocious puberty is caused by early secretion of sex hormones. These sex hormones can be derived from the gonads, adrenal glands, or exogenous sources. Examples of peripheral sources of precocious puberty in girls would be ovarian cysts or tumor. In boys, sources of peripheral precocious puberty include Leydig cell and human chorionic gonadotropin-secreting germ cell tumors. Other sources can be seen in either sex and include primary hypothyroidism, exogenous sex steroids (from exposure to estrogen- or testosterone-containing creams, ointments, or sprays), adrenal tumors, congenital adrenal hyperplasia, and McCune-Albright syndrome.

Delayed Puberty

Delayed puberty is defined as the absence or incomplete development of secondary sexual characteristics by an age that is considered appropriate for 95% of the children of that sex and culture. In the United States, boys who have not had testicular enlargement by age 14 or girls who have not developed breast buds by age 12 are considered to have delayed puberty. Passage of more than 5 years from initial onset of puberty to completion is also considered delayed puberty. Delayed puberty can be caused by constitutional pubertal delay, primary hypogonadism (high circulating levels of LH and FSH), or secondary hypogonadism (low or normal levels of LH and FSH). Appropriate evaluation of a child with suspected pubertal delay includes a complete history including timing of any development of secondary sexual characteristics, physical exam, and growth chart review. Laboratory evaluation should include measurements of LH, FSH, and estradiol (in girls) or testosterone (in boys) and GnRH stimulation test. A radiograph of the left wrist for bone age is also indicated. A magnetic resonance imaging (MRI) of the brain should be performed if a central nervous system lesion is suspected. Causes of primary hypogonadism include Turner's and Klinefelter's syndrome. Examples of secondary hypogonadism are constitutional delay of growth and puberty, GnRH deficiency, disorders of the pituitary or hypothalamus, and functional causes from poor nutrition or chronic disease.

Hypogonadism in Adults

Hypogonadism can occur in both sexes and result in infertility and loss of secondary sexual characteristics. The most common cause in women is menopause which is the natural process of loss of ovarian (gonadal) function. If this process occurs before the age of 40, it is considered premature ovarian failure. Surgical procedures such as oophorectomy can also result in loss of gonadal function. In men, the most causes of gonadal failure are medications, radiation, alcohol, infection, and trauma. Symptoms of hypogonadism include malaise, decrease libido, infertility, loss of secondary sexual characteristics, and depressed mood. In both men and women, FSH and LH levels will be elevated. If secondary hypogonadism is suspected, MRI should be obtained to evaluate for pituitary or hypothalamic mass.

Hirsutism and Virilization

Both hirsutism and virilization are the result of androgen excess. Hirsutism is the excessive growth of hair in a male pattern on the face, axilla, chest, and suprapubic areas. Development of acne can also be seen with hirsutism. Hirsutism affects between 5% and 10% of women of reproductive age [17]. Hirsutism can range from a minor cosmetic issue to the early sign of an adrenal adenocarcinoma. Virilization is defined as androgen-dependent masculinization of women and is characterized by frontal balding, clitoromegaly, increased muscle mass, and deepening of the voice. When virilization occurs with defeminization (decreased breast size and vaginal atrophy), it is always pathological.

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Diagnosis

A thorough history is the first step to determining the cause of hirsutism and virilization [17]. This should include age of onset, symptoms, medications, weight changes, menstrual history, ethnicity, and family history. Physical examination should focus on areas of hair growth, body mass index, signs of virilization, and evidence of defeminization. The skin should be examined for acne, seborrhea, acanthosis nigricans, and striae. The Ferriman-Gallwey score is an evaluation tool which identifies hair growth in 11 areas. A score of 8 or greater confirms hirsutism. An abdominal and pelvic exam shoulder be performed to evaluate for masses that could indicate an androgen-secreting tumor. Laboratory evaluation should include serum total testosterone level. If the level is greater than 200 ng/dL, MRI should be performed to evaluate the adrenal glands and pelvis for mass. If the serum testosterone level is mildly elevated, an ACTH stimulation test can help to differentiate adrenal causes such as 21-hydroxylase deficiency from other causes such as obesity or insulin resistance.

Management

Management of hirsutism and virilization is based on the patient's goals or more emergent treatment of malignant causes [17]. Cosmetic treatments may include shaving, plucking, waxing, or bleaching of unwanted hair growth. Electrolysis and laser therapies are available too but at a higher cost. Eflornithine is a topical medication that may slow hair growth over a period of 4 to 8 weeks. Once stopped, however, the hair growth returns. For women who do not plan to become pregnant, a combined estrogen-progestin oral contraceptive is considered first-line oral medication therapy. The antiandrogen spironolactone maybe added if desired results are not achieved. Insulin-lowering agents are not an effective therapy for hirsutism but maybe used for their other benefits. Flutamide is a nonsteroidal androgen receptor antagonist which has been used off-label for managing hirsutism. Long-acting GnRH agonists may also be used to suppress the hypothalamic-pituitary-ovarian axis.

Calcium Metabolism and Parathyroid Glands

Calcium metabolism is regulated largely by two hormones: parathyroid hormone (PTH) and vitamin D. Calcitonin is another hormone which is produced in response to hypercalcemia by perifollicular cells in the thyroid to inhibit osteoclastic activity. Calcitonin release infrequently leads to hypocalcemia with the rare exception of medullary thyroid tumors. PTH is released by the parathyroid glands which are four small glands located in the neck adjacent to the thyroid. PTH modulates calcium in response to low serum calcium by stimulating osteoclastic activity in bones to free calcium stores, increase calcium resorption in the renal tubules to decrease renal calcium loss, and increase intestinal calcium absorption directly and through renal production of calcitriol. Additionally, PTH is involved in phosphate renal reabsorption inhibition which increases serum calcium.

Hypercalcemia and Hyperparathyroidism

Hypercalcemia is most commonly caused by hyperparathyroidism from benign hyperfunctioning parathyroid adenomas leading to increased bone resorption. While these adenomas account for approximately 80% of primary hyperparathyroidism, idiopathic and familial parathyroid hyperplasia also occur. Other causes include malignancy (including parathyroid carcinomas), hyperthyroidism, prolonged immobilization, Paget's disease, medications (e.g., thiazide diuretics and lithium), sarcoidosis, and vitamin D intoxication.

Clinical Presentation

Hyperparathyroidism and hypercalcemia are commonly identified through routine laboratory testing when an elevated serum calcium is noted.

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Patients may also exhibit symptoms leading to the suspicion of hypercalcemia such as nausea, vomiting, abdominal pain, recurrent nephrolithiasis, bradycardia, polyuria, polydipsia, or muscle atrophy.

Diagnosis

The first step in investigating an elevated serum calcium (usually defined as a serum calcium greater than 10.5 mg/dL) is to confirm through repeat testing with correction for albumin level (0.8 mg/dL of calcium for each 1 g/dL of albumin). Alternatively, ionized calcium levels may be obtained. Once hypercalcemia is confirmed, PTH and 25-OH vitamin D levels should be obtained. Patient history and clinical presentation may also necessitate evaluation for malignancy, particularly if PTH and vitamin D levels are normal. This evaluation could include prostate-specific antigen (PSA) testing, alkaline phosphatase levels, TSH, urinary calcium excretion (particularly if PTH is normal or only minimally elevated), and imaging (e.g., radiographs for sarcoidosis or bone scan if malignancy is highly suspected). The patient's medication list should be reviewed, but one should not assume medication as the primary cause without other negative evaluation.

Management

It is critical to identify the cause of hypercalcemia to institute effective therapy. Consideration for discontinuing offending medications should be given. Vitamin D toxic individuals should have supplement dosages lowered. If hyperparathyroidism is confirmed as the cause, symptomatic patients should have parathyroid surgery [18]. Asymptomatic patients may be considered for surgical evaluation if they meet guidelines from the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism [19]. These include patients whose serum calcium is 1.0 mg/dL or greater than the upper limit of normal, bone density in the osteoporotic range (T-score <-2.5), previous vertebral compression fracture, age less than 50, renal impairment with an estimated GFR of <60 mL/min, recurrent nephrolithiasis or nephrocalcinosis, or 24-h urinary calcium >400 mg/day. Patients not meeting these criteria may reasonably be managed non-operatively but should have serum calcium, renal function, and bone mineral density monitored every 1 to 2 years as up to one-third of patients may show disease progression and develop one of the previously mentioned indications for surgery [20].

Hypocalcemia and Hypoparathyroidism

While hyperparathyroidism causes hypercalcemia, hypoparathyroidism leads to hypocalcemia and hyperphosphatemia. The most common cause for hypoparathyroidism is iatrogenic parathyroidectomy [21]. Other causes of hypocalcemia which may or may not be associated with hypoparathyroidism include gastrointestinal diseases which limit calcium absorption, poor dietary calcium intake, autoimmune disorders, DiGeorge syndrome, vitamin D deficiency, hypomagnesemia, renal disease, and pancreatitis. Rarely infiltrative diseases (Wilson's disease or hemochromatosis) and metastatic cancer can lead to parathyroid destruction and subsequent hypocalcemia. As with hypercalcemia, identifying the underlying cause is paramount to appropriately treating hypocalcemia.

Clinical Presentation

The signs and symptoms of hypocalcemia generally correlate to the severity and are most often neurologic in nature. Mild hypocalcemia may produce no symptoms or produce depression or other psychiatric symptoms. More severe hypocalcemia may produce tetany, paresthesia, carpopedal spasm, delirium, or seizures. Carpopedal spasm may be elicited using a blood pressure cuff pumped up to the patient's systolic blood pressure (Trousseau's sign), and facial muscle hypercontractility (Chvostek's sign) may be

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elicited with tapping on the ipsilateral facial nerve. Hypocalcemia may also be suspected in patients with a prolonged QT interval on ECG.

Diagnosis

As with hypercalcemia, hypocalcemia must be confirmed after correction for serum albumin, which is commonly low in the elderly population. Once confirmed, PTH levels should be checked to assist in determining the underlying cause. Low PTH is most likely from removal or destruction of the parathyroid glands [21]. Magnesium levels should also be checked as hypomagnesemia, or significant hypermagnesemia may cause a functional hypoparathyroid state. Hypocalcemia in the setting of hypomagnesemia can be very difficult to correct. Elevated PTH levels in the setting of low calcium may be associated with vitamin D deficiency, pancreatitis, chronic kidney disease, severe illness or sepsis, or metastasis.

Management

As per hypercalcemia and hyperparathyroidism, treatment should target the underlying cause [22]. In acute, severe hypocalcemia with severe symptoms or ECG changes, intravenous calcium replacement is often indicated with an initial starting dose of 1 to 2 g of calcium gluconate infused over 10 to 20 min. Caution should be used when using IV calcium in patients with impaired renal function. Concomitant hypomagnesemia should be corrected. Management of chronic hypocalcemia or non-severe acute hypocalcemia should be done orally, and vitamin D supplementation implemented if low. Generally, 1.5–2 g of elemental calcium daily can be safely administered and levels monitored, adjusting the dosage as necessary.

Adrenal Dysfunction

The adrenal gland is comprised of the adrenal medulla, 10% of the gland, and the adrenal cortex, 90% of the gland, which is further divided into the zona glomerulosa, zona fasciculata, and zona reticularis. The adrenal medulla secretes the catecholamines epinephrine and norepinephrine. The medulla is linked to the autonomic nervous system.

The zona glomerulosa is 15% of the adrenal cortex and produces mineralocorticoids which are part of the renin-angiotensin system. The primary product of the zona glomerulosa is aldosterone which regulates electrolyte and fluid volume through potassium and magnesium secretion and sodium reabsorption. The zona fasciculata makes up 60% of the cortex and produces glucocorticoids, primarily cortisol, which regulate fat, carbohydrate, and protein metabolism. The zona reticularis makes up the remaining 25% of the cortex and produces sex hormones, e.g., testosterone and estradiol.

Adrenocortical Insufficiency

Primary adrenal insufficiency (Addison's disease) occurs when the adrenal cortex does not produce enough cortisol or aldosterone [23]. The most common etiology is idiopathic autoimmune adrenalitis. Other causes are damage to the adrenal glands, tuberculosis, fungal infections, neoplasia, or amyloidosis. Addison's disease is rare with a prevalence of 100 to 140 cases per million in the Western society, most commonly at ages 30 to 50 years [23].

Secondary adrenal insufficiency is classified as hyposecretion of ACTH from the pituitary which causes reduced cortisol levels. The most common etiology of secondary insufficiency is exogenous steroid use which leads to the suppression of the hypothalamic-pituitary-adrenal axis (HPA axis).

Clinical Presentation

The onset of Addison's disease is typically chronic, and patients may not seek medical attention in early disease [23]. Signs and symptoms are the results of gluco- and mineralocorticoid deficiency. Signs include weight loss, orthostatic hypotension due to dehydration, hyponatremia, hyperkalemia, anemia, and hypoglycemia. Nonspecific symptoms of Addison's disease are weakness, fatigue, musculoskeletal pain, weight loss, abdominal pain, depression, and anxiety. Some patients may have salt

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craving. Increased secretion of ACTH may lead to hyperpigmentation of the skin and mucous membranes; patients with pale skin generally have associated hypopituitarism.

Due to delay in treatment, the initial clinical presentation may occur when a patient is in acute life-threatening adrenal crisis. Signs and symptoms of adrenal crisis include severe weakness, syncope, acute abdominal pain, and hypotension leading to shock, renal failure, and death. Secondary adrenal insufficiency can present as moderate symptoms to severe adrenal crisis [24]. Abrupt discontinuation of corticosteroids after long-term treatment (e.g., Cushing's syndrome, sarcoidosis, rheumatoid arthritis) can also lead to adrenal insufficiency.

Diagnosis

Patients who present with symptoms suggestive of adrenal insufficiency (e.g., volume depletion, hypotension, hyponatremia, hyperkalemia, fever, abdominal pain, hyperpigmentation, and hypoglycemia) should be tested for primary adrenal insufficiency [23]. A low 8:00 AM serum cortisol (less than 5 mcg/dL) with mentioned symptoms suggests adrenal insufficiency. Plasma ACTH can be measured at the same time as serum cortisol to aid diagnosis. Lack of cortisol production from the adrenal cortex should be confirmed with an ACTH stimulation test. To confirm decreased adrenal cortisol production, patients are administered 0.25 mg ACTH intravenously, and serum cortisol levels are measured at baseline, 30, 60, and 90 min. Peak cortisol levels less than 18 mcg/dL at 30 or 60 min are indicative of adrenal insufficiency. Addison's disease presents with low cortisol levels and persistently elevated plasma ACTH (more than twofold the upper limit of normal). A specialist referral should be considered to aid in the etiology or diagnosis of Addison's disease.

Management

The first-line treatment for Addison's disease is hydrocortisone (15–25 mg in two or three divided doses orally) as it has both glucocorticoid and mineralocorticoid effects [23]. Oral cortisone acetate is another first-line option. Hydrocortisone should be given at awakening and either 2 h after lunch (2 daily doses) or at lunch and in the afternoon (3 daily doses). For noncompliant patients, prednisolone may be given either once or twice daily. All patients with confirmed aldosterone deficiency should have mineralocorticoid replacement with fludrocortisone (50–100 mcg daily) and no restriction on salt intake. If patients develop hypertension on fludrocortisone, the dose should be decreased, and antihypertensives initiated if necessary.

Monitoring involves clinical assessment with body weight, blood pressure, and energy levels. Patients with suspect adrenal crisis should be immediately treated with parenteral hydrocortisone followed by fluid resuscitation and a continuous IV hydrocortisone infusion over 24 h. Treatment of suspected adrenal crisis should not be delayed by diagnostic confirmation. Every patient should have an emergency glucocorticoid injection kit (injection or per rectum) and wear medical identification.

Adrenocortical Excess

Adrenocortical excess (Cushing's syndrome) symptoms result from either endogenous or, more commonly, exogenous increases in glucocorticoids [25]. Exogenous Cushing's syndrome occurs with the administration of glucocorticoids. Endogenous etiologies can be caused by ACTH overproduction (ACTH-dependent) by a pituitary adenoma (Cushing's syndrome), a glucocorticoid-producing adrenal adenoma or carcinoma, or other neoplasm (usually lung, thyroid, or pancreas). Less common causes are independent of ACTH usually with adrenal adenoma or carcinoma etiologies.

Clinical Presentation

Cushing's syndrome is primarily characterized by facial rounding (moon faces) and truncal obesity with a prominent dorsal cervical fat pad (buffalo hump) [25]. Other characteristics include hypertension, hirsutism, osteoporosis, glucose

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intolerance, hypokalemia, abdominal striae (reddish purple color greater than 1 cm), and psychiatric disturbances. Symptoms include proximal muscle weakness, menstrual abnormalities, and sexual dysfunction.

Diagnosis

Diagnosis of adrenocortical excess, or Cushing's syndrome, involves establishing hypercortisolism and then determining the etiology [25]. Patients who have unusual features for their age have multiple progressive features or have adrenal incidentaloma; suspect of adenoma should have a clinical workup for Cushing's syndrome. The primary care physician should first confirm hypercortisolism with lab work; however, iatrogenic causes of hypercortisolism (e.g., administration of glucocorticoids) should be excluded before lab work is obtained. Typical tests are the measurement of 24-h free urine cortisol (UFC) or a low-dose dexamethasone test (DST); other options include measuring late-night salivary cortisol, midnight plasma cortisol, or a longer low-dose DST. For the low-dose DST, patients are instructed to take 1 mg of dexamethasone between 11:00 PM and midnight; a serum cortisol level is then obtained at 8:00 AM the next morning. A normal response to DST is a serum cortisol less than 1.8 mcg/dL; some use a threshold of less than 5 mcg/dL, but it has a lower test sensitivity.

Once hypercortisolism is established, physiologic causes should be excluded including pregnancy, depression, alcohol dependence, glucocorticoid resistance, obesity, or diabetes mellitus. An endocrinology consult should be obtained for further evaluation to confirm or exclude diagnosis and determine the etiology.

Management

Once the diagnosis is confirmed, treatment of Cushing's syndrome involves normalizing cortisol levels to eliminate signs and symptoms and treating comorbidities [25]. If possible, resection of the primary lesion is the preferred treatment option; radiation and chemotherapy can also be used. If surgery is not possible or if patients decline, glucocorticoid antagonists can be used as second line to normalize cortisol levels. Different pharmacotherapy options are available for ectopic ACTH syndrome, pituitary-dependent, and adrenal adenomas or carcinomas.

Hyperaldosteronism

Primary hyperaldosteronism, or Conn syndrome, is a rare condition caused by an aldosterone-secreting neoplasia or hyperplasia of the adrenal gland [26]. Secondary hyperaldosteronism is associated with renin hypersecretion (e.g., renal artery stenosis). Primary hyperaldosteronism is a common secondary form of arterial hypertension with a particularly high prevalence among patients with resistant hypertension.

Consensus guidelines recommend a workup for primary aldosteronism in patients with resistant hypertension (sustained elevated blood pressure while on the maximum dose of three antihypertensives of which one is a diuretic); controlled hypertension but on four or more antihypertensives; hypertension and diuretic-induced hypokalemia, adrenal incidentaloma, sleep apnea, or a family history of cerebrovascular accident at a young age (less than 40 years); hypertension and a first-degree relative with primary aldosteronism. The plasma aldosterone/renin ratio (ARR) is used to detect possible cases. Patients should be referred to endocrinology for confirmatory testing and imaging after a positive ARR test; however, confirmatory testing is not needed with spontaneous hypokalemia or plasma renin below detection levels with plasma aldosterone concentration (PAC) >20 ng/dL. Adrenal computed tomography scan and adrenal venous sampling (AVS) can distinguish between unilateral and bilateral primary aldosteronism and adrenal hyperplasia.

First-line treatment for unilateral primary aldosteronism is surgery. In bilateral pulmonary aldosteronism, or if patients decline surgery, mineralocorticoid receptor antagonists (e.g., spironolactone or eplerenone) are used for treatment. Mineralocorticoid receptor antagonists should be used at the lowest effective dose with

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low sodium diets to normalize blood pressure and potassium [27].

Hypoglycemia

Overview

Hypoglycemia in adults is usually caused by medications used to treat diabetes mellitus. Other causes include critical illness, hormone deficiency (e.g., cortisol), nonislet cell tumor, or endogenous hyperinsulinism. In the absence of diabetes mellitus treatment, hypoglycemia must be confirmed with the presence of Whipple's triad: symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after the plasma glucose concentration is raised [28]. Confirmation with Whipple's triad prevents expensive and unnecessary evaluation. Hypoglycemia is generally defined as a plasma glucose concentration of less than 70 mg/dL, severe if less than 55 mg/dL. However, individuals will have varied physiologic responses to low plasma glucose concentrations. Symptoms of hypoglycemia are either neurogenic (autonomic nervous system response) or neuroglycopenic (result of low brain blood glucose concentrations). Neurogenic symptoms include palpitations, tremor, anxiety, sweating, and hunger. Neuroglycopenic symptoms are behavioral changes, fatigue, confusion, diplopia, seizure, and loss of consciousness which can lead to death.

Diagnosis

A thorough workup should be completed for patients with Whipple's triad-confirmed hypoglycemia in the absence of diabetes mellitus [28]. The general differential should include a careful medication history as drugs are the most common cause of hypoglycemia. The most common drug culprits are insulin, insulin secretagogues, and alcohol. Some uncommon medication causes of hypoglycemia are angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, beta blockers, and fluoroquinolones. Acute illness such as sepsis and renal or hepatic failure should be ruled out. Cortisol deficiency-associated hypoglycemia is rare. In symptomatic patients, plasma measurements of glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and insulin antibodies can help distinguish between endogenous and exogenous causes of hypoglycemia. An increase in plasma glucose in response to administered glucagon 1.0 mg IV can help identify insulin-mediated hypoglycemia. Endogenous hyperinsulinism presents as high levels of insulin, C-peptide, and proinsulin at low fasting plasma glucose concentrations.

A diagnostic approach involves a supervised 72-h fast where all medications are stopped and plasma glucose, insulin, C-peptide, and proinsulin are measured at specified intervals. The fast is completed once the patient develops symptoms of hypoglycemia with corresponding hypoglycemic plasma glucose. An endocrine consult should be obtained after confirmation of postprandial endogenous hyperinsulinemic hypoglycemia without endogenous agents or circulating insulin antibodies to help identify the insulinoma.

Management

Treatment is dependent on the specific hypoglycemia disorder. Offending exogenous causes (e.g., alcohol, medications known to cause hypoglycemia) of hypoglycemia should be limited as appropriate [28]. Patients with a history of gastric surgery or gastric bypass are prone to hypoglycemia secondary to hyperinsulin response; eating smaller but more frequent meals can alleviate hypoglycemia. Exercise-induced hypoglycemia may be treated by carbohydrate loading before and during exercise. Insulinomas are extremely rare and may require surgical treatment. The severity of hypoglycemia should be considered before invasive treatment.

Gout

Gout is the most common form of inflammatory arthritis with a prevalence of approximately 9.2 million adults in the United States [29]. It is caused by a deposition of monosodium urate

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crystals in tissue and joints; however, visualization of these crystals is not required for diagnosis. Risk factors include cardiovascular disease, diabetes mellitus, hyperlipidemia, chronic kidney disease, as well as specific dietary and demographic factors. Treatment is available for acute attacks as well as urate-lowering therapy for long-term management. Lifestyle changes, especially reduction in purine-rich foods such as organ and glandular meat, are important for a good prognosis.

Clinical Presentation

Gout is a form of arthritis which presents as acute or chronic. Acute gout, referred to as a "gout flare," presents as a sudden onset of severe pain, swelling, warmth, and erythema of synovitis. The most commonly affected joint is the first metatarsophalangeal joint, the podagra. Gout flares are self-limiting, peak within 12 to 24 h, and resolve over 1 to 2 weeks even without treatment. Chronic tophaceous gout occurs if gout flares occur at short intervals without complete resolution of symptoms that cause joint destruction. Common signs of chronic gout are uric acid tophi which are deposits of uric acid in periarticular fibrous tissue and in the cartilage of the ear and kidneys. Patients may have asymptomatic hyperuricemia; no treatment is recommended for these patients.

Diagnosis

Synovial fluid analysis for detection of monosodium urate crystals is the gold standard in confirming the diagnosis [30]. However, it should be reserved for patients who are suspected of having a septic joint, in which a culture and gram stain of the aspirate should be performed, in addition to analysis of monosodium urate crystals. Serum uric acid levels may be normal in patients with acute gout. There are several algorithms that can aid in the diagnosis of gout clinically without invasive joint aspirations. These algorithms include the Rome and New York Criteria, ARA Criteria, Janssens Diagnostic Rule, Clinical Gout Diagnosis Criteria, Monoarthritis of the First Metatarsophalangeal Joint, Study for Updated Gout Classification Criteria (SUGAR), and the 2015 ACR/European League Against Rheumatism Gout Classification Criteria. Another method of diagnosis is imaging such as sonography and dual-energy computerized tomography.

Management

First-line treatment for acute gout flares includes nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine [29]. Oral colchicine or glucocorticoids may be used when NSAIDs are contraindicated such as in comorbid cardiovascular disease, chronic kidney disorder, or cerebrovascular disease. A typical NSAID and dose are naproxen 500 mg twice daily which is equivalent to prednisolone 35 mg orally daily. Low-dose colchicine should be administered within 24 h (less efficacy if within 36 h) of symptom onset at a dose of 1.2 mg followed 0.6 mg 6 h later. Colchicine 0.6 mg daily should be continued until resolution of gout flare. High-dose colchicine should not be used as it has similar efficacy to low-dose colchicine but with increased adverse effects such as diarrhea. When oral administration is not feasible, glucocorticoids may be given via the intramuscular, intravenous, or intraarticular route. Topical ice may be used as an adjuvant to pharmacologic therapy of a gout flare.

Urate-lowering therapy is recommended for patients who have $\geq$1 subcutaneous tophi, evidence of radiographic damage related to gout, or $\geq$2 gout flares annually. Urate-lowering therapy may be considered in patients with a history of more than one gout flare. Urate-lowering therapy should not be initiated during a gout flare as it can lead to worsening of symptoms. Allopurinol with a starting dose of 100 mg daily is the preferred first-line treatment even for patients with moderate-to-severe chronic kidney disease. Allopurinol should be titrated weekly by 100 mg increments to a serum uric acid level $<$6 mg/dL. Some experts prefer treating serum uric acid to $<$5 mg/dL [31]. Slow titration of allopurinol helps to avoid gout flares [29]. In addition, concomitant

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anti-inflammatory prophylaxis with NSAIDs, colchicine, or corticosteroids to avoid flares is recommended for 3 to 6 months after starting urate-lowering therapy. Before starting allopurinol, patient of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African Americans should be tested for HLA-B*5801 allele. Allopurinol is contraindicated in patients carrying the allele. Febuxostat is an alternative to allopurinol-intolerant patients, but it should be avoided in patients with a history of cardiovascular disease or with a new cardiovascular event. Pegloticase has been approved as an alternative in patients with refractory gout.

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Part XXV

The Blood and Hematopoietic System

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Anemia

130

Daniel T. Lee and Monica L. Plesa

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Background and Introduction

Anemia is a reduction in blood hemoglobin (Hgb) concentration or hematocrit (Hct). Normal values of Hgb and Hct vary based on age, gender, ethnicity, and other special considerations and have been widely studied over the years. Data from large samples selected to represent the population of the United States suggests that the lower limit of normal hemoglobin concentrations be 13.7 g/dL in young white men (ages 20–59 years) and

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12.9 g/dL in young black men; 13.2 g/dL in white and 12.7 g/dL in black men ages 60 years and over; and 12.2 g/dL in white women and 11.5 g/dL in black women 20 years and over, including elderly women [1]. The lower limit of normal for children age 1–3 years is 11 g/dL, with the cutoff rising to approach adult values by age 15–19 years. Between 2003 and 2012 data from five National Health and Nutrition Examination Surveys estimated that 5.6% of the United States' population had anemia based on the World Health Organization's criteria, with pregnant women, women of reproductive age, the elderly, non-Hispanic blacks, and Hispanics at highest risk [2].

It can be particularly difficult to diagnose the cause of anemia in the elderly population, and between 30% and 50% of anemia in this age group can be considered "undiagnosed anemia of the elderly" after extensive workup [3]. People residing at higher altitudes have higher baseline Hgb and Hct levels than residents at sea level. Smokers and patients exposed to significant secondhand smoke may have higher Hgb and Hct levels as well [4]. Endurance athletes can have a "sports anemia" as a result of increased plasma volume that lowers hematocrit despite stimulated erythropoiesis and higher red blood cells counts (RBCs) compared to sedentary individuals [5]. Gastrointestinal (GI) bleeds, anemia of chronic inflammation (ACI) due to increased cytokine release with exercise, hemolysis of senescent RBCs in contracting or compressed muscles, hematuria, and sweating can further contribute to this "sports anemia," especially in long distance runners [5, 6]. Additionally, it is always important to evaluate results in the context of previous data. For example, a low "normal" Hgb may be significant if a recent value was higher.

On occasion, the Hgb and Hct may not accurately reflect red cell mass as they are concentrations and depend on the plasma volume. For example, patients with expanded plasma volume, as in pregnancy or congestive heart failure, may have falsely low values while patients with plasma contraction, as in burns or dehydration, may have falsely elevated values. In the setting of acute blood loss, both RBCs and plasma are lost equally, and the true degree of anemia may not be appreciated until plasma volume has time to expand.

Anemia may be categorized by the RBC size (microcytic, normocytic, or macrocytic) or by cause (RBC underproduction, RBC destruction, or RBC loss). A patient's history, physical exam, and laboratory studies are integral to determine the etiology of the anemia regardless of the diagnostic approach taken.

Clinical Presentation

Symptoms

Symptoms of anemia are highly variable, and depend on the degree of anemia and the rapidity of its development. They arise from the effects of decreased oxygen delivery to end organs and can be exacerbated by hypovolemia. In response to a decrease in Hct, the body increases oxygen extraction by its tissues as well as increases the delivery of oxygen to these tissues by augmenting cardiac output with a faster heart rate and larger stroke volume. Those with mild or gradually developing anemias may be seemingly asymptomatic, although these patients may also demonstrate symptoms that are not yet recognized by the patient and/or physician [7]. Others may present with a range of symptoms including fatigue, weakness, decreased exercise tolerance, dizziness, headache, tinnitus, palpitations, syncope, impaired concentration, and restless leg syndrome (RLS). Some patients experience abdominal discomfort, nausea, and bowel irregularity as blood is shunted from the splanchnic bed. Children with anemia may present with impaired cognitive or psychomotor development. Decreased blood flow to the skin may result in cold intolerance. Patients with preexisting vascular disease are prone to exacerbations of angina, claudication, or cerebral ischemia.

History

Historical clues assist in determining the cause of anemia. Family history of anemia or onset of anemia in childhood suggests an inherited etiology. Chronic medical conditions such as hepatic, renal, endocrine, or inflammatory disorders can lead to anemia of chronic disease (ACD). Malignancies

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and infections may also cause anemia. Exposure to some medications, alcohol, and toxins (e.g., lead) can lead to anemia due to bone marrow suppression or interference with vitamin absorption. Chronic diarrhea or a history of GI conditions associated with malabsorption suggests a nutritional deficiency anemia. Obesity or a history of bariatric surgery or other GI surgeries can predispose to iron deficiency anemia (IDA). Dietary intake of iron, folate, and vitamin B12 (cobalamin) should be obtained. Paresthesias of the extremities or alteration in mental status may point to vitamin B12 deficiency. A history of gallstones or jaundice points to hemolysis. Pica is the craving for nonfood items frequently seen with iron deficiency. Patients will often crave ice, or earthy items such as clay or soil, or raw starches such as corn starch or raw rice among multiple other substances. Potential blood loss from the GI tract or heavy uterine bleeding must be ascertained. Frequent blood donations or blood draws in hospitalized patients may lead to an induced anemia.

Physical Examination

Tachycardia and wide pulse pressure may be present in the anemic patient as a result of increased cardiac output. The skin and conjunctiva may demonstrate pallor. In very severe anemias, retinal hemorrhages may be seen. Jaundice may suggest hemolysis or liver disease. Glossitis can be present in vitamin B12 and iron deficiency. Lymphadenopathy may occur in the presence of hematologic malignancies and infections such as HIV and tuberculosis. A systolic ejection murmur and venous hum may be heard. Signs of liver disease and splenomegaly should be sought. Proprioception and balance deficits may occur in vitamin B12 deficiency. The stool may be examined for blood.

Laboratory Data

Complete Blood Count. Once a patient is determined to be anemic by Hgb and/or Hct, a complete blood count (CBC) with differential should be obtained for the RBC indices as well as the platelet and white blood cell (WBC) values. Mean corpuscular volume (MCV) reflects the size of the RBC. The normal MCV for adults is debatable, with the lower limit of normal defined as 80–82 fl and the upper limit of normal as 98–100 fl. MCV in children is lower, starting at 70 fl at 1 year of age and increasing 1 fl/year until adult values are reached at puberty. Table 1 divides common causes of anemia into microcytic (<82 fl), normocytic (82–98 fl), and macrocytic (>98 fl).

The red cell distribution width (RDW) quantitates the variation in size of the RBCs. Normal RDW is less than 14.5%. An elevation of the RDW may make the MCV by itself less reliable. An example is a patient who has both iron and B12 deficiencies. In this case, the MCV may be normocytic, but the RDW will be elevated [8]. Data obtained from ICU and cardiac patients suggests a possible correlation between increased RDW and increased inflammation, oxidant damage, or vascular trauma that may be predictive of poor outcomes irrespective of the presence of anemia [9].

Mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) generally mirror the MCV (i.e., smaller RBCs tend to have lower MCHs and MCHCs, such as in iron deficiency and thalassemias). Larger RBCs tend to have greater MCH and MCHC values, such as in spherocytosis or sickle cell anemia.

The presence of hypochromic and hyperchromic RBCs is also important in evaluating anemia. Hypochromic erythrocytes (MCHC <28 g/dL) tend to be more prevalent in IDA than in thalassemias while hyperchromic erythrocytes (MCHC >41 g/dL) can easily identify hereditary spherocytosis [9].

Platelet and WBC counts should be noted. Among other things, decreased platelet levels (thrombocytopenia) and/or decreased WBCs (leukopenia) suggest bone marrow suppression, aplastic anemia, hypersplenism, vitamin B12 deficiencies, infections, or malignancies. Elevated platelet counts (thrombocytosis) are often seen in IDA, trauma, and infections. Increased WBC counts (leukocytosis) can also be seen in infections and malignancies. Severe pancytopenia should prompt a workup for aplastic anemia, hematologic malignancy, or chemotherapy and/or radiation side effects, among other causes.

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Table 1 Classification of Anemia Based on MCV

Microcytic	**Macrocytic**
Iron deficiency	Non-megaloblastic
Thalassemia	Alcoholism
Anemia of chronic disease*	Chronic liver disease
Hemoglobin E*	Bone marrow disorders
Sideroblastic anemia*	Hypothyroidism*
Lead poisoning*	Sideroblastic anemias*
Hereditary*	Marked reticulocytosis
Myelodysplastic syndrome*	Spurious*
Severe alcoholism*	Normal variant*
Medications*	Neonatal period
Normocytic	Megaloblastic
Elevated reticulocyte count	Folate deficiency
Acute blood loss	Poor intake
Hemolysis	Malabsorption
Pregnancy	Ethanol
Decreased reticulocyte count	Medications
Anemia of chronic disease	Pregnancy
Chronic kidney disease	Infancy
Chronic liver failure	High folate requirement
Endocrine disease	B12 (cobalamin) deficiency
Iron deficiency	Pernicious anemia
Myelodysplastic syndromes	Gastric or ileal surgery*
Aplastic anemia*	Ileal disease*
Pure red cell aplasia*	Strict veganism*
Myelophthisic anemia*	Fish tapeworm infection*
Sideroblastic anemia*	Bacterial overgrowth*
	Pancreatic insufficiency*
	Medications* (anticonvulsants, chemotherapy, zidovudine)
	Congenital disorders*

*less common

Reticulocyte Count. Reticulocytes, which are newly formed RBCs, normally account for about 1% of circulating RBCs. Reticulocyte formation is increased in a normal individual who loses blood, with the degree of reticulocytosis increasing as anemia becomes more severe. Therefore, a patient's reported reticulocyte percentage should be adjusted for the degree of anemia to determine if the bone marrow response is appropriate:

$$\text{corrected reticulocyte}\% = \text{reticulocyte}\% \text{x } \text{patient's Hct}/\text{normal Hct}.$$

A corrected reticulocyte percentage (also known as reticulocyte index) greater than 1% indicates appropriate bone marrow response to anemia. If the value is less than 1%, causes of hypoproliferative bone marrow should be sought. Increased reticulocyte counts are present in hemolysis, acute hemorrhage, and response to treatment in anemias from other causes. An alternative to corrected reticulocyte percentage is the absolute reticulocyte count, which equals the reported reticulocyte percentage multiplied by the RBC count. The absolute reticulocyte count is normally 50,000–75,000/mm^3.

Peripheral Smear. Abnormalities in the peripheral smear, such as burr cells seen in renal failure or tear drop cells found in myelofibrosis, can assist in determining the etiology of anemia.

Other Laboratory Tests. Further laboratory testing may be warranted, depending on the above RBC indices and peripheral smear. Bone marrow biopsy is reserved for situations in which anemia remains unexplained or is suspected to arise from marrow dysfunction. Algorithms for evaluation of microcytic, normocytic, and macrocytic anemias are provided in Figs. 1, 2, and 3.

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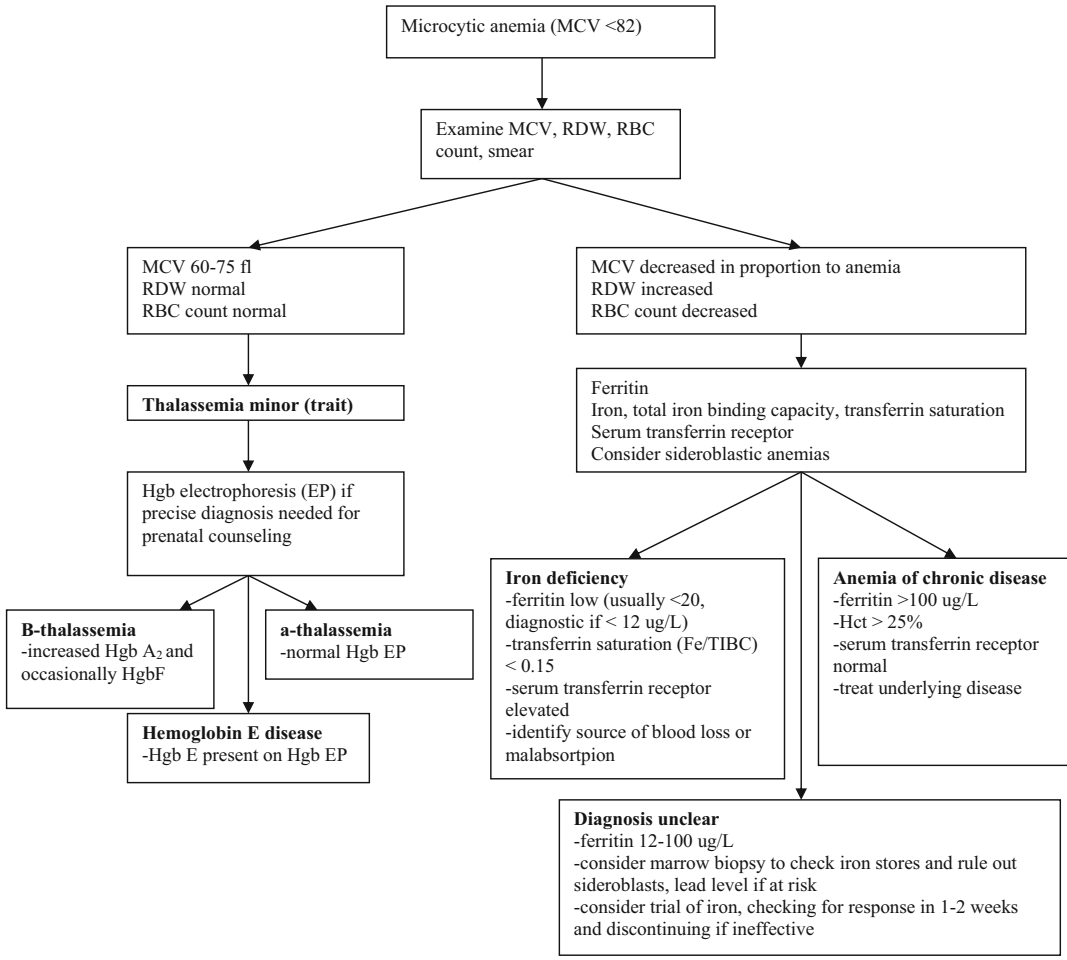


Fig. 1 Evaluation of microcytic anemia

Microcytic Anemias (Fig. 1)

Iron Deficiency Anemia

IDA is probably the most common cause of anemia in the world, accounting for about half of all cases [10]. The recommended dietary allowance (RDA) for iron is 8 mg daily for men and 18 mg daily for women [11]. Daily requirements increase during pregnancy, lactation, and adolescence. Meats, eggs, vegetables, legumes, and cereals are principal sources of iron in the American diet, with iron from meats being much more available for absorption than iron from other dietary sources.

In the United States, approximately 4% of children aged 5 months to 4 years old were found to be anemic between 2003 and 2012, with prevalence varying based on race/ethnicity. IDA accounts for approximately 40% of anemia in children, with Hispanic children ages 1–3 years old twice as likely to have IDA compared to black and white children in this age group [2]. Term, healthy infants have sufficient iron stores for at least the first 4 months of life. However, breast milk does not contain as much iron as does formula, so full term infants who are exclusively or mostly breastfed may become iron deficient around 4–6 months of age until they receive sufficient iron through solid food sources. Therefore, iron supplementation of 1 mg/kg/day may be

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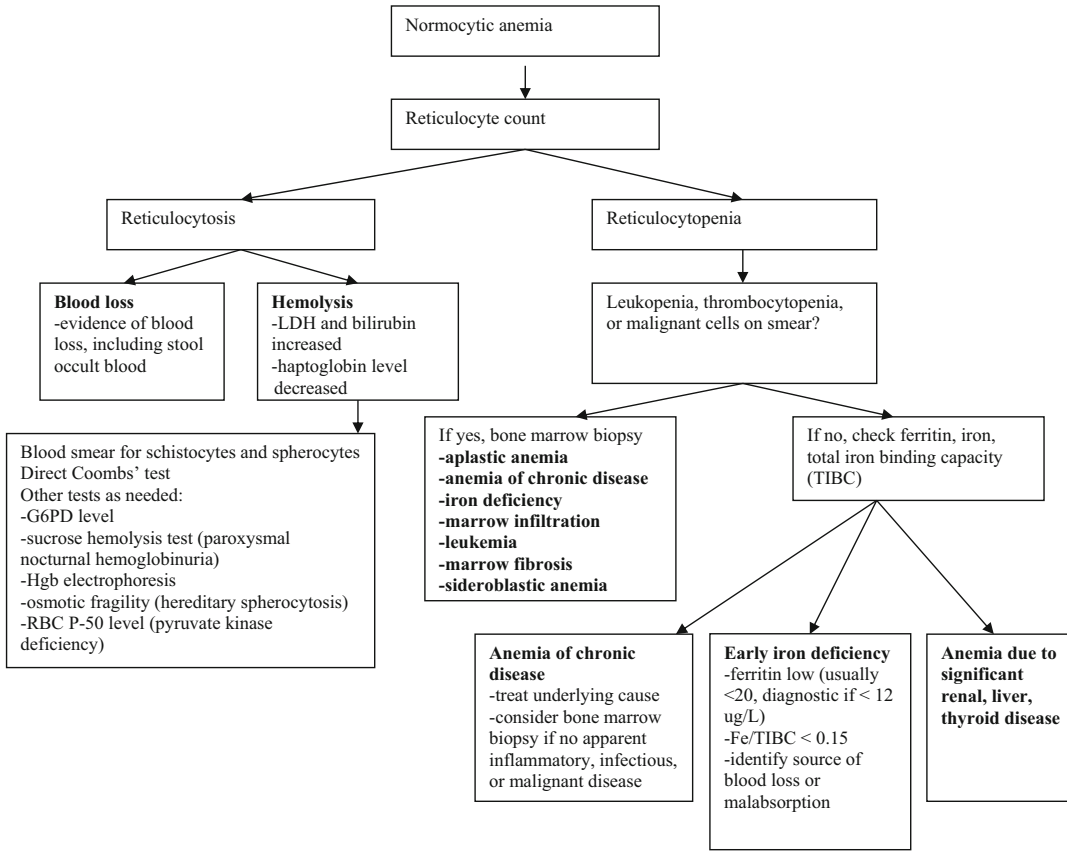


Fig. 2 Evaluation of normocytic anemia

considered in these infants starting at 4 months of age until appropriate iron-containing complementary foods (including iron-fortified cereals) are introduced into the diet.

IDA may also be seen in older infants fed primarily cow's milk because the iron content is low and cow's milk may displace other sources of iron in these infants' diets. Furthermore, the high levels of calcium and phosphorous in cow's milk can decrease iron absorption. Thus, the American Academy of Pediatrics recommends screening for anemia in all infants around 12 months of age [12]. A serum ferritin and C-reactive protein level (CRP) should be checked if patient is anemic. Elevations of both ferritin and CRP can occur in the setting of inflammation. On the other hand, a low serum ferritin (<12 ug/L) confirms IDA, and these infants should be treated appropriately. Alternatively, infants with mild anemia (10–11 dL/g) can undergo a trial of iron supplementation for 1 month, and a repeat Hgb showing an appropriate rise of 1 dL/g would confirm IDA [12].

Other populations that may develop IDA include children and adolescents whose iron needs are increased due to their rapidly growing bodies in conjunction with poor iron intake. Females lose iron in menstrual blood and can become iron deficient if their bleeding outpaces their iron intake. Pregnancy places additional demands on a woman's iron stores as the placenta and fetus require iron and blood is lost during childbirth. Obesity can predispose to IDA due to increased inflammation from adipose tissue and subsequent increased production of hepcidin, which directly impairs absorption of iron and iron availability for erythropoiesis. Patients with a history of bariatric surgery are at risk of IDA given their history of obesity and possible

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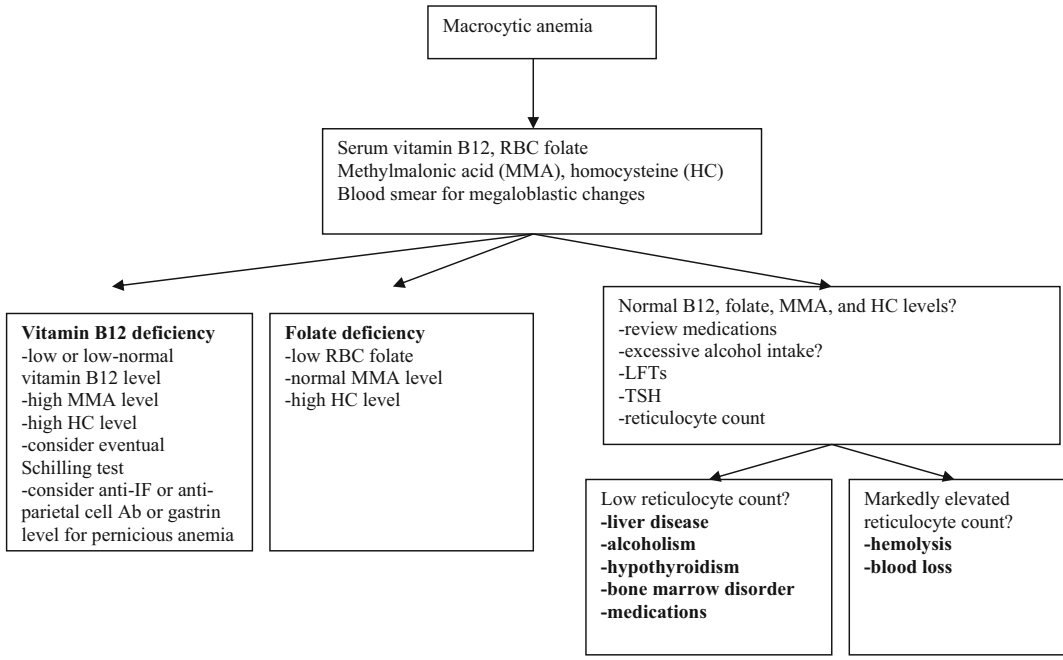


Fig. 3 Evaluation of macrocytic anemia

malabsorption resulting from the surgery itself [13]. IDA is also seen in decreased absorption states such as celiac disease and prior bariatric or other GI surgeries.

In men and postmenopausal women, GI blood loss is the most likely cause of IDA. In these patients, a diligent search for occult GI bleeding is imperative when another source of bleeding is not readily appreciated. This should include upper and lower endoscopy with small bowel biopsy. Radiologic tests may substitute if endoscopy is not practical. In over one-third of patients with IDA, no source of blood loss will be found despite this evaluation [14]. In these patients, prognosis is good, with anemia resolving in more than two-thirds without recurrence [15]. Further search for source of GI blood loss is required only for persistent bleeding or severe anemia.

Physician examination may reveal glossitis and angular stomatitis. Esophageal webs, splenomegaly, and koilonychias (spoon-shaped nails) rarely occur. Patients may complain of RLS. Although the relationship is unclear, one study showed 24% of patients with IDA also had RLS [16].

The most sensitive and specific laboratory test for IDA is serum ferritin, which reflects iron stores. While a ferritin below 12 ug/L is diagnostic, a workup for IDA should be considered in patients with ferritins of 13–20 ug/L since a significant number of these patients will have IDA. Since ferritin is an acute phase reactant, falsely normal levels may occur with coexisting inflammatory conditions. Normal ferritin values also increase with age and must be considered when evaluating anemia in an older adult. Nonetheless, a ferritin level above 100 ug/L practically rules out IDA [17]. A decreased serum iron and increased total iron binding capacity (TIBC) are helpful but less reliable indicators of IDA. The transferrin saturation (iron/TIBC) should be less than 0.15, but this ratio may be reduced in ACD as well. The MCV is usually normal in early iron deficiency and typically decreases after the Hct drops. The MCV then changes in proportion to the severity of anemia. The RDW is often increased. Although not as widely available, soluble serum transferrin receptor (TfR) rises in IDA and may assist diagnosis in difficult cases, although an increase in

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TfR may also be seen in increased or ineffective erythropoiesis [18, 19]. The transferrin receptor-ferritin index (ratio of TfR to the logarithm of serum ferritin) may also play a role in these difficult cases, with a value >2 suggesting IDA and a value <1.0 indicating ACD [20].

Occasionally, ferritin values fall in the indeterminate range of 12–100 ug/L and the diagnosis remains uncertain. Bone marrow biopsy is the gold standard to determine iron stores but is rarely necessary. An alternative is a several week trial of iron replacement. Reticulocytosis should peak after 1 week and the Hct should normalize in about a month. If no response to therapy occurs, iron should be discontinued to prevent potential iron overload and iron therapy side effects.

Oral iron replacement is available in ferrous and ferric forms. Ferrous forms are preferred due to superior absorption and include ferrous sulfate, gluconate, and fumarate. Although most patients with IDA may not need this much, ferrous sulfate 325 mg TID (65 mg of which is elemental iron) is the cheapest and provides the theoretically needed 150–200 mg of elemental iron per day in patients with IDA. Some studies suggest that much less iron supplementation is needed in patients with IDA as their GI tracts absorb more iron after becoming iron deficient. Thus, as little as 60 mg elemental iron once or twice a week may suffice if the patient is unable to tolerate daily dosing [20]. Although Hct should normalize in a few weeks, iron replacement should continue until ferritin reaches 50 ug/L or at least 4–6 months. Many patients experience side effects of nausea, constipation, diarrhea, or abdominal pain as a result of activated hydroxyl radicals released during the oxidation of ferrous compounds within the lumen of the gut or the mucosa [7]. Enteric-coated iron preparations are meant to decrease these symptoms but are not well absorbed and should be avoided. To minimize these effects, iron may be started once a day and titrated up. In addition, iron may be taken with food, although this can decrease absorption by 40–66% [21]. Taking iron with vitamin C may help increase absorption [22]. Liquid iron preparations may be tried. Despite these measures, 10–20% of patients will not tolerate oral iron replacement [23]. Bran, eggs, milk, tea, caffeine, calcium-rich antacids, H_2-blockers, proton pump inhibitors, and tetracycline can interfere with iron absorption and should not be taken at the same time. Also, iron supplementation can interfere with the absorption of other medications, including quinolones, tetracycline, thyroid hormone, levodopa, methyldopa, and penicillamine.

Most patients respond well to oral replacement of iron. Treatment failures may result from poor adherence, continued blood loss, interfering substances listed above, or gastrointestinal disturbances limiting absorption. In the rare case where poor absorption or severe intolerance to iron cannot be overcome, parenteral replacement may be needed. Iron dextran may be given IV or as a painful IM injection. The total dose (mg) required to replenish stores equals:

$$0.3 \times \text{body weight (lb)} \times (100 - \text{Hgb [g/dL]} \times 100)/14.8$$

Adverse reactions include headache, flushing, dyspnea, nausea, vomiting, fever, hypotension, seizures, and chest, back, and abdominal pain. Urticaria and anaphylaxis can occur. A test dose (0.5 ml = 12.5 mg) should be given to determine whether anaphylaxis will occur. If tolerated, the remainder of the dose may be given up to a maximum daily dose of 100 mg over 2 min or more. If possible, intravenous iron is preferred over intramuscular due to a lower incidence of local reactions and more consistent absorption.

Thalassemia

The thalassemias are inherited disorders of hemoglobin synthesis that are more common in people from the Mediterranean, Asia, and Africa. The rare thalassemia majors cause severe anemia and are discovered early in life. Family physicians are more likely to encounter thalassemia trait (thalassemia minor) occurring in individuals heterozygous for alpha or beta globin chain mutations.

Thalassemia trait should be suspected in an asymptomatic patient with mild anemia and a disproportionately low MCV (56–74 fl). The

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RDW is usually normal and the RBC count is normal or increased by 10–20%. Iron studies are normal unless concomitant IDA is present. Blood smear may show target cells, ovalocytes, and basophilic stippling. If a precise diagnosis is required (for prenatal counseling, for example), hemoglobin electrophoresis may be performed. In beta thalassemia trait, elevated levels of Hgb A2 and occasionally Hgb F will be seen. In alpha thalassemia trait, the hemoglobin electrophoresis will be normal, and the diagnosis is made by exclusion. It is important to determine the etiology of anemia in these patients as treatment with iron therapy is unnecessary and potentially harmful in patients with thalassemia trait who do not have IDA.

Hemoglobin E

Hgb E has a prevalence of 5–30% in certain groups from Southeast Asia. The heterozygote has mild microcytosis and normal Hct. Homozygotes have marked microcytosis (MCV 60–70 fl) and mild anemia. Target cells may be present on peripheral smear. Hgb electrophoresis reveals the presence of Hgb E, establishing the diagnosis. Patients who have both Hgb E and beta thalassemia develop severe transfusion-dependent anemias.

Sideroblastic Anemia

Sideroblastic anemias are a heterogeneous group of disorders in which ringed sideroblasts are found on bone marrow staining. Sideroblastic anemia may be X linked or due to toxins or medications (lead, alcohol, isoniazid, chloramphenicol, chemotherapy). It may be related to neoplastic, endocrine, or inflammatory diseases or a part of myelodysplastic syndrome. The MCV is usually low but may range from low to high. Iron saturation and ferritin are normal to high. Marrow examination is diagnostic and treatment is aimed at the underlying cause. In the case of lead poisoning, anemia is microcytic and basophilic stippling may be seen on peripheral smear. This diagnosis should be suspected and serum lead level tested in high-risk groups such as children ingesting paint, soil, and dust, and adults with occupational exposure.

Normocytic Anemias (Fig. 2)

The absolute reticulocyte count or corrected reticulocyte percentage is important in determining the cause of a normocytic anemia.

Normocytic Anemia with Elevated Reticulocytes

Acute Blood Loss. Acute blood loss is usually obvious but can be missed in cases such as hip fractures and retroperitoneal or pulmonary hemorrhages. The true degree of anemia may not be revealed in the Hct at first, since RBCs and plasma are lost equally. It may take several days for equilibration of blood volume and Hct to fully reflect the degree of bleeding.

Hemolysis. There are many causes of hemolytic anemia (Table 2). Laboratory values consistent with hemolysis include elevated serum lactate dehydrogenase (LDH) and indirect bilirubin. Haptoglobin, a plasma protein that binds and clears Hgb, drops precipitously in the presence of hemolysis. If hemolysis is suspected, the peripheral smear should be examined for schistocytes (mechanical hemolysis) and spherocytes (autoimmune hemolysis or hereditary spherocytosis). A direct Coombs' test will reveal an autoimmune basis for hemolysis. Further confirmatory testing may be performed as appropriate (Fig. 2), usually with the guidance of a hematologist. Treatment of hemolytic anemia is directed at the underlying cause and providing supportive care. Corticosteroids and splenectomy may be indicated for specific causes.

Pregnancy. Pregnancy can result in a physiologic anemia as a woman's blood volume expands by approximately 50% while her red blood cell mass increases by only 25%. As a result pregnant women require approximately 1 additional gram of iron daily. Because IDA during pregnancy has

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Table 2 Causes of hemolysis

Intrinsic (defect in RBCs)	Extrinsic (defect external to RBCs)
Hemoglobinopathies sickle syndromes unstable hemoglobins methemoglobinemia	Immune autoimmune lymphoproliferative malignancy collagen vascular disorders drug induced (methyldopa, procainamide, quinidine, levodopa, sulfas, penicillin, NSAIDS)
Membrane disorders paroxysmal nocturnal hemoglobinuria hereditary spherocytosis elliptocytosis pyropoikilocytosis stomatocytosis	Mechanical disseminated intravascular coagulation (DIC) thrombotic thrombocytopenia purpura (TTP) hemolytic uremic syndrome (HUS) prosthetic heart valves disseminated neoplasms burns malignant hypertension vasculitis severe hypophosphatemia physical activity ("march" hemoglobinuria) strenuous exercise
Enzyme deficiencies glucose-6-phosphate dehydrogenase (G-6-PD) pyruvate kinase glucose phosphate isomerase congenital erythropoietic porphyria	Hypersplenism
	Infections Clostridium, Plasmodium, Borrelia, Mycoplasma, Babesia, Hemophilus, Bartonella
	Bites snakes spiders

been associated with adverse maternal-fetal outcomes including an increased risk of low birth weight, preterm delivery, and perinatal mortality, pregnant women found to have IDA should be treated with supplemental iron. Those who do not respond to iron supplementation should be further evaluated [24].

Normocytic Anemias with Decreased Reticulocytes

Anemia of Chronic Disease. ACD, also called anemia of chronic inflammation (ACI), results from chronic inflammatory disorders, infections, and malignancies. ACD is the second most common cause of anemia after iron deficiency. It is probably the most common form of anemia in the elderly [25]. The pathogenesis of ACD is multifactorial and not fully understood. Proposed mechanisms include reduction in RBC life span, impaired utilization of iron stores, and a relative erythropoietin deficiency. Although the anemia is customarily normocytic, it can be microcytic in 30–50% of cases [26]. The degree of anemia is usually mild, with Hgb between 7 and 11 g/dl. The serum iron, TIBC, and transferrin saturation are usually low and not helpful in distinguishing ACD from IDA. More useful is the ferritin level, which is normal or high in ACD. Ferritin greater than 100 ug/L essentially rules out IDA, whereas levels less than 12 ug/L are diagnostic of IDA. In cases of uncertain ferritin levels (12–100 ug/L), a brief therapeutic trial of iron or a bone marrow biopsy may help with the diagnosis. Normal TfR levels may be useful in diagnosing ACD due to the suppression of TfR by inflammatory cytokines [17].

Treatment of ACD is directed toward management of the underlying disorder. Erythropoietin plus iron supplementation is effective in raising Hct in certain cases. Iron treatment by itself is not indicated for ACD since iron stores are adequate. However, if the anemia is more severe than expected, one should search for a coexisting cause. For example, a patient with rheumatoid

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arthritis may develop concomitant IDA from GI blood loss due to chronic NSAID use.

Chronic Kidney Disease. Anemia occurs frequently in chronic kidney disease (CKD) due primarily to the kidney's inability to secrete erythropoietin. Generally, the creatinine is above 3 mg/dl or the estimated glomerular filtration rate (eGFR) is less than 30 ml/min/1.73 m^2. The peripheral smear is usually normal, but burr cells can be seen. The ferritin is typically increased. If a low to low-normal ferritin is noted, concomitant IDA should be entertained. In fact, many patients with end stage kidney disease may suffer from "functional iron deficiency." The Kidney Disease: Improving Global Outcomes guidelines recommends considering iron repletion in patients with CKD with anemia and serum transferrin saturation $\leq$30% and ferritin $\leq$500 μg/L. [27]

Therapy consists of ameliorating the renal disease and administering erythropoiesis-stimulating agents (ESAs), namely erythropoietin and darbapoietin. ESA should be considered for non-hemodialysis patients with CKD and Hgb < 10 g/dl, with a goal Hgb of 10–11.5 g/dl. Initial dosing of ESA is based on the patient's Hgb concentration, body weight, and clinical circumstances, and it is adjusted based on the patient's response to treatment. The FDA recommends starting Epoetin alfa at 50–100 units/kg three times per week; however, more commonly it is dosed at 10,000 units weekly or 20,000 units every other week. Patients with concomitant IDA should have iron repleted prior to and during ESA therapy in order to prevent worsening IDA and enhance erythropoiesis. Iron stores should be assessed at least every 3 months during treatment [27]. The treatment and dosing of ESA with iron supplementation may be performed in consultation with a hematologist and/or nephrologist. Hemodialysis may improve RBC production, but ESA is the mainstay of treatment, even before dialysis is required. Blood transfusions should be minimized. Complications of ESAs include increased blood pressure.

Chronic Liver Disease. Chronic liver disease causes a normocytic or occasionally macrocytic anemia. Target cells can be seen on peripheral smear. Spur cells are seen in severe liver failure. Treatment is directed at improving liver function. Alcoholics with liver disease have additional causes for anemia that are discussed under non-megaloblastic macrocytic anemias.

Endocrine Disease. Various endocrine diseases such as hypothyroidism, hyperthyroidism, hypogonadism, hypopituitarism, hyperparathyroidism, and Addison's disease are associated with anemia. The anemia is corrected with treatment of the underlying endocrine problem.

Aplastic Anemia. Aplastic anemia is due to an injury or destruction of a common pluripotential stem cell resulting in pancytopenia. Bone marrow biopsy reveals severe hypoplasia and fatty infiltration. In the United States, approximately half the cases are idiopathic. Other causes include viral infections (HIV, hepatitis, EBV), drugs and chemicals (chemotherapy, benzene, chloramphenicol), radiation, pregnancy, immune diseases (eosinophilic fasciitis, hypoimmunoglobulinemia, thymoma, thymic carcinoma, graft-versus-host disease), paroxysmal nocturnal hemoglobinuria, systemic lupus erythematosus, and inherited disorders.

Treatment includes managing the underlying cause and supportive care in conjunction with a hematologist. Judicious use of transfusions may be needed if the anemia is severe. Immunosuppressive therapy and bone marrow transplantation are indicated in certain cases.

Myelophthisic Anemia. Myelophthisic anemias result from bone marrow infiltration by invading tumor cells (hematologic malignancies or solid tumor metastases), infectious agents (tuberculosis, fungal infections), or granulomas (sarcoidosis). Less common causes include lipid storage diseases, osteopetrosis, and myelofibrosis. Treatment is directed at the underlying cause.

Red Cell Dysplasia. Pure red cell dysplasias involve a selective failure of erythropoiesis. The granulocyte and platelet counts are normal. Red cell dysplasias share many causes with aplastic and myelophthisic anemia, including malignancies, connective tissue disorders, infections, and drugs. There is an idiopathic form and a congenital form. One infection that specifically targets red cell production is parvovirus B19. This virus also causes erythema infectiosum ("fifth" disease), an

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acute polyarthropathy syndrome, and hydrops fetalis. Anemia results from parvovirus B19 infection mostly in those with chronic hemolysis, by suppressing erythropoiesis and disrupting a tenuous balance needed to keep up with RBC destruction. In this situation, anemia can be profound but is usually self-limited. Parvovirus B19 infections may become chronic in immunosuppressed individuals who cannot form antibodies to the virus. Treatment concepts for red cell aplasia are similar to treatments for aplastic anemia.

Myelodysplastic Syndromes. The myelodysplastic syndromes (MDS) are a group of clonal hematologic diseases of unknown etiology that result in the inability of bone marrow to produce adequate erythrocytes, leukocytes, platelets, or some combination of these. Patients are usually over 60 years of age and have an increased risk for leukemia. MDS may account for as much as 15–20% of anemia in the elderly [3]. Bone marrow biopsy is diagnostic, revealing characteristic dysplastic blood precursor cells. Treatment is largely supportive.

Macrocytic Anemias (Fig. 3)

Macrocytic anemias may be separated into megaloblastic and non-megaloblastic types, based on peripheral smear findings (Table 1). A sensitive and specific sign of megaloblastic anemia is hypersegmented neutrophils, in which neutrophils contain nuclei with more than five lobes. A marked elevation of MCV (>120 fl) is also highly suggestive of megaloblastosis. RBCs of megaloblastic anemias, in addition to being increased in size, are often oval in shape (macroovalocytes).

Most macrocytosis, however, results from non-megaloblastic causes. Drug therapy and alcoholism may account for >50% of macrocytosis, whereas vitamin B12 and folate deficiencies may be responsible for only 6% of cases [28].

Megaloblastic Anemias

Vitamin B12 Deficiency. Vitamin B12 (cobalamin) is ingested from primarily animal sources, including meats, eggs, and dairy products. The US RDA of vitamin B12 increases with age and is 2.4 ug daily for adults. A typical Western diet provides 5–30 ug/day. After ingestion, B12 is bound by intrinsic factor, which is produced by gastric parietal cells. Bound vitamin is absorbed in the terminal ileum. Body stores of vitamin B12 total 2,000–5,000 ug. Thus, B12 deficiency takes years to develop and rarely occurs from dietary insufficiency except in strict vegans. The majority of B12 deficiency is due to pernicious anemia, which occurs primarily in the elderly and is most often due to autoimmune atrophy of the gastric mucosa and intrinsic factor deficiency. Less often, pernicious anemia can be due to *H. pylori* infections or Zollinger-Ellison syndrome. Other causes of B12 deficiency include gastric and ileal surgeries, including gastric bypass surgery and ileal absorption problems such as Crohn's disease, sprue, tapeworm infection, and medications such as metformin, proton pump inhibitors, H2-blockers, and antacids.

Signs and symptoms of B12 deficiency include glossitis, sore mouth, and GI disturbances such as constipation, diarrhea, and indigestion. Neurologic symptoms such as paresthesias of the extremities and subacute combined degeneration (loss of lower extremity vibration and position sense) may occur. Dementia and subtle neuropsychiatric changes may be present. Importantly, anemia or macrocytosis are absent in 28% of patients with neurologic abnormalities due to B12 deficiency [29].

In addition to peripheral smear changes of hypersegmented neutrophils and macroovalocytes, laboratory findings include a low B12 level (<200 pg/ml) and reticulocyte count. However, low normal B12 levels (<350 pg/ml) are present in many patients with neurologic disease or anemia, so further workup may be indicated if the diagnosis is still suspected. Falsely low B12 levels may be found in folate deficiency, pregnancy, and myeloma. Elevated serum methylmalonic acid (MMA) levels are highly sensitive and essentially rule out B12 deficiency if normal. In one study, elevated MMA levels occurred in 98% of cases of clinically defined B12 deficiency. Falsely elevated levels occur in

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kidney disease and hypovolemia, and spot urine MMA levels may be superior in this setting. Homocysteine level rises with B12 deficiency (96% of cases in one study) but are less specific, occurring in folate deficiency and kidney disease as well [30–32]. Occasionally, a mild thrombocytopenia and leukopenia, along with an elevated LDH and indirect bilirubin from ineffective erythropoiesis, are present.

Traditionally, the Schilling test was performed to determine the etiology of B12 deficiency. It measures 24-h urinary excretion of radiolabeled B12 given orally and distinguishes pernicious anemia from bacterial overgrowth and other absorption problems. This test is not commonly utilized as it is expensive, difficult to perform properly, and no longer available in many centers. Antibodies to intrinsic factor may be measured and are the preferred test for diagnosing pernicious anemia. These antibodies are highly specific for pernicious anemia but present in only about 50% of cases. Antibodies to gastric parietal cells are found in about 85% of cases of pernicious anemia but also in 3–10% of healthy persons [32]. Extremely elevated serum gastrin levels and low pepsinogen 1 levels also suggest pernicious anemia.

B12 replacement regimens vary. One common method is 1,000 ug vitamin B12 IM daily for 1 week, then weekly for 1 month, and then every 1–3 months. The Hct should return to normal in 2 months. Failure to normalize should trigger a search for coexisting iron deficiency, which occurs in up to one-third of patients. Six months or more may be needed for neurologic improvement and up to 80% of patients will have at least partial resolution of neurologic manifestations. An alternative to parenteral B12 is high dose oral therapy. Patients with pernicious anemia can absorb 1–2% of oral B12 without the addition of intrinsic factor, so treatment with daily oral B12 1,000–2,000 ug can be considered in adherent patients [33]. B12 maintenance can also be accomplished with an intranasal gel preparation 500 ug once weekly, although this form is more costly than parenteral and oral forms. Treatment should continue indefinitely as the deficiency will likely return unless a reversible cause is identified and addressed.

Folate Deficiency. Folate is found in a wide variety of unprocessed foods. Especially rich sources include green leafy vegetables, citrus fruits, liver, and certain beans and nuts. The RDA for folate is about 200 ug daily and is increased to 400 ug in pregnancy. In contrast to vitamin B12, folate stores remain adequate for only 2–4 months, so folate deficiency anemia is often the result of inadequate dietary intake. The typical Western diet provides only 200–300 ug of folate daily. Persons at risk for folate deficiency include malnourished alcoholics, neglected elderly, and the homeless. Patients who are pregnant or have certain malabsorption disorders are also at risk. Impaired absorption may occur in patients taking oral contraceptives, metformin, methotrexate, or antibiotics such as trimethoprim or pyrimethamine or anticonvulsants, such as phenytoin, valproate, and carbamazepine. Cirrhosis can lead to deficiency through decreased storage and metabolism capabilities of the liver. Dialysis can cause loss of folate and deficiency.

The clinical findings of folate deficiency are similar to B12 deficiency except neurologic symptoms are generally absent. The laboratory findings are similar except that the homocysteine level alone is elevated while MMA remains normal. The serum folate can rise to normal after a recent folate rich meal, vitamin ingestion, or hemolysis, so serum folate should not be used for diagnosis. Although expensive, RBC folate level is felt to be more accurate. Confirmation with homocysteine levels should be obtained if the diagnosis is suspected.

Treatment is aimed at the underlying problem. Replacement is usually 1 mg orally daily. If present, concurrent vitamin B12 deficiency must be treated as well, because folate replacement can resolve hematologic abnormalities while permitting neurologic damage from vitamin B12 deficiency to progress.

Drugs. Certain drugs cause megaloblastic anemia. Most common causes are chemotherapy agents. Infrequent causes are phenytoin, sulfasalazine, zidovudine, trimethoprim, pyrimethamine, methotrexate, triamterene, sulfa compounds, and oral contraceptives.

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Non-megaloblastic Anemias

Alcoholism. The most common cause of non-megaloblastic macrocytic anemia is alcoholism. Anemia in alcoholics may arise from multiple causes. Alcohol suppresses erythropoiesis and decreases folate absorption in patients whose diets are often poor. Alcoholics can lose blood from varices and ulcers. Anemia is worsened if liver failure occurs. Moreover, alcoholics are prone to develop sideroblastic or hemolytic anemia. They are also at increased risk for developing infections that can lead to ACD. Comprehensive therapy includes reduction of alcohol intake, folate supplementation, and treatment of complications.

Miscellaneous. The anemia of hypothyroidism, chronic liver disease, post-splenectomy, and primary bone marrow disorders may be macrocytic instead of normocytic. Hemolytic anemia or hemorrhage can result in macrocytosis when reticulocytes, which are larger than normal RBCs, are markedly increased. Certain drugs occasionally cause non-megaloblastic macrocytic anemia. Spurious macrocytosis, although rare, must also be considered due to cold agglutinins causing the RBCs to clump and appear larger to automated counters. Other causes include hyperglycemia causing RBCs to swell when diluted during blood processing or leukocytosis leading to increased blood sample turbidity with a subsequent overestimation in cell size by the machine [34].

Summary

Discovery of anemia should lead the physician to investigate its underlying cause. Conversely, it may be reasonable to check for anemia in patients who develop certain acute or chronic medical conditions. The history and physical examination combined with the CBC, peripheral smear, and reticulocyte count reveal the etiology in most cases. However, it is not uncommon to find multifactorial causes for a patient's anemia. If the type of anemia remains unclear or there is additional evidence of marrow dysfunction (pancytopenia), a bone marrow biopsy and hematology consultation may be indicated.

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Selected Disorders of the Blood and Hematopoietic System

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Emily Emmet, Anusha Jagadish, Rajat Malik, and Raj Mehta

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Bleeding Disorders

Bleeding disorders can be present in both adult and pediatric populations. Diagnosing a suspected bleeding can be a difficult task in hematology. However, with the combination of a good history, diagnostic approach and understanding of various disorders, a diagnosis and management plan can be made [1].

Patients can present in many waves, ranging from easy bruising to excessive bleeding. As stated before, a family history is key in identifying bleeding disorders. A positive family history is a good indicator warranting further work-up. Additional history like diet and medications can also lead a physician to a correct diagnosis, ruling out iatrogenic causes [2].

Once the suspicion is high, blood work should be done to either confirm or dismiss the diagnosis. Labs include complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), bleeding time, and platelet function assay. Patients can also be referred to a hematologist for further work-up and management, especially if lab findings are normal but there is a high clinical concern.

Management of bleeding disorders is based on the comfort level of both the physician and the patient. It can become complex, and referral to Hematology at the time of diagnosis is appropriate. Ultimately, a patient-centered approach is important and associated with improvement in level of functioning and compliance.

Congenital Coagulation Disorders

Von Willebrand's Disease

One of the most common bleeding disorders, Von willebrand's Disease (vWD), has a prevalence as high as 1.5%. It is defined by a deficiency of von Willebrand factor (vWF), a glycoprotein that mediates adhesion of platelets to sites of vascular damage [2]. It is inherited in an autosomal dominant pattern, affecting males and females equally. It is also common to have low levels of Factor VIII with vWD [3].

Symptoms of hemorrhage include epistaxis, gastrointestinal bleeding, easy bruising, menorrhagia, postpartum bleeding, Gastrointestinal (GI) bleeds, hemarthrosis, and bleeding after trauma or procedures like dental extraction. Type III is usually much more severe compared to Type I and II. Most individuals never come to get medical attention for bleeding because the disease is often mild.

Complete blood count with platelet PT and PTT are usually normal. vWD can be confirmed with the laboratory findings of decreased Factor VIII levels and activity, decreased vWF activity, and decreased vW antigen. Bleeding time is no longer used due to its time-consuming nature and that it does not correlate with bleeding risk. vWF Ristocetin cofactor assay is the gold standard for platelet-binding activity. vWWF activity to vWF antigen ratios are then used to further characterize the type and severity of von Willebrand disease [4].

When treating vWD, the goal is to prevent bleeding and correct coagulation abnormalities. There are different methods of treating based on severity and contact of bleeding. vWF concentrates and recombinant vWF can be used for major life-threatening bleeding. DDAVP (desamino-D-arginine vasopressin) is a medication that works by increasing plasma levels of vWF, Factor VIII, and tissue plasminogen activator (t-PA) [5]. Patients with mild vWD can be treated with DDAVP 0.2–0.3 mcg/kg administered intravenously or 150–300 mcg intranasally. Antifibrinolytic agents and Factor VIII can be used in adjunct to these treatments. Platelet transfusion for those with thrombocytopenias is also a consideration. Oral contraception can also be used in females who have menorrhagia due to vWD, it

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causes increased levels of Factor VIII and vWF. Surgical and dental procedures can be performed in most patients, starting treatment 1 h prior and up to 2–3 days after. vWD can be preventable through genetic counseling; there is a 50% chance of children with a parent with vWD at risk of developing it [3].

Hemophilia A

Hemophilia A is a bleeding disorder caused by a deficiency in Factor VIII. It's mode of transmission and gene expression is X-linked recessive; therefore, males have Hemophilia A and females are asymptomatic carriers. All daughters of fathers with the disorder will be carriers and all their sons will be normal, where male children of a mother who carries the gene have a 50% chance of having the disease. Hemophilia A affects approximately 1/10,0000–20,000 males in the United States [6]. Initial presentations in children include easy bruising, hemarthrosis, oral bleeding, and post-procedural bleeding within the first year of life.

Factor VIII is involved in the clotting pathway. Its deficiency results in larger sites of bleeding like hemorrhage into muscles or joints. Severe hemophilia will present within a year and a half of life. Common bleeding also includes genitourinary tract, central nervous system, gastrointestinal tract, and oral cavity. Unlike platelet disorders, excessive bleeding after minor cuts or abrasions is not common. When screening bleeding disorder, there is a prolonged activated aPTT. Other coagulation tests like platelet count, bleeding time, and PT are all normal. To confirm the diagnosis, a serum Factor VIII activity level <40% or 0.40 IU/mL [7].

It is important to institute integrated care once a diagnosis is made, as this disease can be complex, routine, and comprehensive care is important [6]. Newborns should follow normal immunization schedules. Dental care is important to prevent gum and tooth disease, which increase the chances of bleeding. Anticoagulants, Aspirin, and NSAIDs should be avoided. Special considerations must be taken when a patient with hemophilia has any surgery or procedure done: done at a facility with an adequate blood bank and transfusion services, experienced surgeons in treating those with coagulopathies, discussion with hematologist and anesthesiologist, no intramuscular medications, avoidance of salicylate, and maintenance of Factor VIII levels.

The goal of treatment is to increase levels of Factor VIII. Hemorrhage is prevented by infusion of recombinant or human-derived Factor VIII. Serum Factor VIII level is targeted based on symptoms: 0.3 U/mL for patients with minor hemorrhage, 0.5 U/mL with severe hemorrhage, and 0.8–1.0 U/mL. However, treatment of choice is intravenous desamino-D-arginine vasopressin (DDAVP) (Desmopressin acetate 0.3 ug/kg) for patients with mild hemophilia [8]. E-Aminocaproic acid (EACA), a potent inhibitor of fibrinolysis, can also be used as a single or adjunctive postoperative dose (4 g PO q4–6hrs for 2–8 days for dental procedures [9]).Ultimately, genetic counseling and testing women who are at risk for carriers can help prevent future generations with Hemophilia A.

Hemophilia B

Hemophilia B is a bleeding disorder caused by a deficiency in Factor IX. It is an X-linked recessive inheritance pattern. This disorder has an incidence of about 1/30,0000 males. It is diagnosed via a Factor IX assay.

Clinically, Hemophilia B is almost indistinguishable from Hemophilia A, the same clotting cascade is affected. Diagnosis is based on Factor IX activity. Treatment includes intravenous human-derived or recombinant Factor IX concentrate. You can also treat the disorder with Fibrinolytic factors. Unlike Hemophilia A, DDAVP has no value in treatment [5].

Easy Bruising

Ecchymosis, or a bruise, is a collection of blood beneath the skin resulting from extravasation from surrounding vessels. Easy bruising is reported in about 18% of the population, predominantly affecting women [8]. It can be considered mostly

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normal when other life-threatening or pathological causes have been ruled out. There are some characteristic lesions however that can be identified.

For example, senile purpura is a lesion of the elderly caused by progressive loss of collagen in vessels and skin likely due to sun exposure. These lesions occur on the upper extremities, especially on the dorsal aspect. They are described as large, dark purple, and well-demarcated. Senile purpuras is a clinical diagnosis. Coagulation studies are usually normal. There is no specific treatment, lesions usually resolve slowly. Counseling the patient and limiting sun exposure may minimize skin changes of aging.

Etiology of bruising is classified into disorders of blood vessels and tissue, platelet abnormalities, and coagulation disorders [8]. These disorders are discussed in this chapter. When evaluating easy bruising, a thorough history, physical exam, and associated trauma are important to know. If warranted, laboratory tests include CBC, PT, aPTT, platelet function. When abnormalities are found, further testing can be done to explore avenues that explain lab findings.

Acquired Coagulation Disorders

Vitamin K Deficiency

Vitamin K is an essential part of the clotting pathway, involved in the synthesis of Factors II, VII, IX, and X. It is a fat-soluble compound that comes from our diet (Especially green leafy vegetables) and is also synthesized by intestinal bacteria [10]. Daily adult requirement of Vitamin K is 100–200 ug/day. Newborns are born with a deficiency because they lack intestinal bacteria to synthesize it. The elderly, those with liver disease, cystic fibrosis, malabsorption syndromes, patients on warfarin, and other long-term medications that disrupt flora can become deficient too.

Vitamin K deficiency presents with bleeding from mucosal surfaces or skin, internal bleeding is less likely. Work-up will be significant for prolonged PT, with a normal bleeding time and platelet count; sometimes aPTT can be prolonged. Usually correcting Vitamin K deficiency can be diagnostic as well. A direct laboratory assay for Vitamin K available as well [10].

Treatment includes replenishing Vitamin K, can be given IV, IM, or PO. If there is life-threatening hemorrhage, fresh frozen plasma is given. The goal of therapy is to prevent further bleeding and correct PT. A diet with adequate Vitamin K and careful use of long-term antibiotics can prevent a deficiency. Newborns are given Vitamin K 0.5–0.1 mg IM to prevent hemorrhagic disease of the newborn. Supplementation can be useful when on anticonvulsant therapy or prolonged treatment with antibiotics. It is important to remember that for the elderly, Vitamin K deficiency can be a sign of neglect or poor diet [10].

Thrombocytopenia

Thrombocytopenia is identified by a low-platelet count below 50,000/μL [11]. It typically occurs due to decreased platelet production or increased platelet destruction. Common causes include liver disease and medication-induced thrombocytopenia. Redistribution and hypersplenism are also possible culprits. Heparin-induced thrombocytopenia (HIT) should be suspected for anyone with falling platelet counts while on heparin. Two forms often presenting with rash and spontaneous bruising include immune thrombocytopenic purpura and thrombotic thrombocytopenic purpura. Disseminated intravascular coagulation is a more severe cause of thrombocytopenia associated with sepsis, trauma, cancer, etc. Treatment of thrombocytopenia depends on identifying the underlying cause and severity of the disease [11].

Hereditary Hemorrhagic Telangiectasia (HHT)

Hereditary Hemorrhagic Telangiectasia (HHT), formerly known as Osler-Weber-Rendu Disease, is a congenital disorder that results in small vessel malformations in the skin and mucosa, creating telangiectasias. It is an autosomal dominant

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disorder that affects males and females equally [12]. The most common presentations are GI bleeds or epistaxis. The lesions become apparent in the second and third decade of life; lesions would be visible in the mouth, face, hands, and feet. They are described as spider-like, round, red-purple, and about 1–3 mm in diameter. Lesions can also occur in almost any organ, however, mostly found in the lungs. Diagnosis is usually made with history and physical exam, there is usually a positive family history. Coagulation studies are usually normal. Treatment is applying pressure to the bleeding sites, or cautery and surgery therapy of lesions if need be. GI bleeding can be stopped by either resection or embolectomy. Unfortunately, HHT is not preventable [13].

Neutropenia

Neutropenia is defined by an absolute neutrophil count less than 1500/mm^3. Absolute neutrophil count (ANC) can be calculated by the following: ANC = WBC × (%bands + %mature neutrophils) × 0.01 [14]. This definition holds true for males, females, and many ethnicities with the exception of children less than 12 months of age, in which case neutropenia is defined by ANC <1000/mm^3. Certain nationalities, including those of African descent, Jewish Yemenites, and some Arab populations, typically have lower ANC counts than the general population (around 1400/mm^3), but will rarely fall below 1000/mm^3. The diagnosis should be confirmed by repeating complete blood count with manual differential and peripheral smear. There are three major causes of neutropenia: decreased production, increased destruction, and margination of neutrophils from blood to tissue. If neutropenia coexists with thrombocytopenia, anemia, and/or abnormalities noted on peripheral smear, further investigation should be pursued in the form of bone marrow aspiration to determine if there are any underlying blood cell line disorder or bone marrow pathology [15].

Neutropenic patients should be referred to hematology for further management after the diagnosis is confirmed. If a neutropenic patient develops fever, broad-spectrum antibiotics must be initiated while awaiting culture results and antibiotic sensitivity. There are certain situations that warrant immediate evaluation in the inpatient setting for a patient with neutropenia, such as signs of sepsis, hemodynamic instability, and respiratory compromise. Patients with ANC <500/mm^3 and/or worrisome findings on peripheral smear (blasts, schistocytes) should also be evaluated in the inpatient setting for prompt diagnosis and treatment. If the patient has moderate (>500 but <1000) neutropenia, is asymptomatic, and has no worrisome findings on peripheral smear, CBC may be repeated in 1–2 weeks to confirm and verify that the neutropenia is true. If the patient has mild >1000 neutropenia and is asymptomatic, CBC may be repeated in 2–6 weeks in the outpatient setting. Granulocyte colony-stimulating factor can be given to stimulate the production of neutrophils in order to reduce the duration of neutropenic fever. It may also be given chronically for the long-term treatment of primary neutropenia.

Acquired Neutropenia

Postinfectious Neutropenia

The most common cause of acquired neutropenia is postinfectious neutropenia [16]. The underlying mechanism of why infections cause neutropenia can be explained by the macrophage activation syndrome (MAS). This occurs when macrophages become activated in response to certain stimuli and the degree by which this happens may be sufficient enough to cause splenomegaly and cytopenias. This occurs after either bacterial or viral infections. Two common bacteria that are associated with neutropenia are *Staphylococcus aureus* and *Escherichia coli*. Additional bacterial infections known to cause neutropenia rather than leukocytosis in some instances are typhoid fever (may also cause pancytopenia), Shigella enteritis, Brucellosis (coexisting anemia is common), Tularemia, and Tuberculosis. Viral infections that are commonly known to cause neutropenia are Epstein–Barr virus, Hepatitis B, cytomegalovirus,

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and influenza. Neutropenia is common among those patients with HIV/AIDS. The degree of neutropenia can be directly correlated to the severity of infection, for example. in sepsis, the neutropenia may be more severe. ANC will typically normalize as the infection resolves.

Drug-Induced Neutropenia

Drug-induced neutropenia is the second most common cause of acquired neutropenia (Table 1). The estimated incidence of idiosyncratic drug reactions is 1/10,000 to 1/100,000. The drugs that are known to commonly cause agranulocytosis are clozapine, thionamides (methimazole), sulfasalazine, and ticlopidine.Treatment of drug-induced neutropenia involves removing the offending drug and consulting a hematologist if the neutropenia does not resolve [17].

Congenital Neutropenia

Congenital neutropenia, also known as "Severe congenital neutropenia" refers to neutropenia that is present at or near the time of birth and is due to a primary bone marrow failure syndrome involving primarily the myeloid series [15]. The incidence is rare, occurring in 2–3 cases per million. There are a variety of mutations that cause SCN and inheritance may be recessive, dominant, or X-linked depending on the mutation. Kostmann syndrome results from mutations in the *HAX1* gene and has an autosomal recessive inheritance. The *HAX1* gene is responsible for maintaining the inner mitochondrial membrane potential and protecting against apoptosis in myeloid cells.

About 50–60% of patients with SCN have mutations in the gene for neutrophil elastase which is an autosomal dominant condition. Cyclic neutropenia is a subtype of inherited neutropenia which is also associated with mutations in this gene (ELANE). Patients will typically present with fever, malaise, and mucosal ulcerations every 3 weeks, with otherwise good health in between episodes. The incidence is 1 case per million in the general population.

The mechanism of neutropenia is due to activation of excessive apoptosis in myeloid precursors. The expression of neutropenia in SCN may be either homogeneous or variable, suggesting different pathogenetic mechanisms and effects of interacting genes. Patients will clinically present with oropharyngeal problems, otitis media, respiratory infections, and skin infections. Oral ulcerations and painful gingivitis are very common in 2 years of age. Diagnosis of SCN is made in an infant with an average absolute neutrophil count of <200/μL with elevated monocytes. Treatment includes granulocyte-colony stimulating factor or hematopoietic stem cell transplantation if severe. The introduction of G-CSF has allowed these patients to live into adulthood but with additional consequences. Patients with SCN have a

Table 1 Drugs that can cause neutropenia

Nonchemotherapy	Chemotherapy
Clozapine	Alkylating agents
Dapsone	Anthracyclines
Hydroxychloroquine	Antimetabolites
Infliximab	Camptothecins
Lamotrigine	Epipodophyllotoxins
Methimazole	Hydroxyurea
Oxacillin	Mitomycin C
Penicillin G	Taxanes
Procainamide	Vinblastine
Quinidine/Quinine	
Rituximab	
Sulfasalazine	
Trimethoprim-sulfamethoxazole	
Vancomycin	

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predisposition to myelodysplastic syndrome and leukemia. The development of these conditions appears to be a complication of the underlying disease rather than a side effect of treatment with G-CSF [18].

Autoimmune Neutropenia

Autoimmune neutropenia is thought to be caused by granulocyte-specific antibodies and has been associated with various underlying disease including infection, collagen vascular disease, or other primary abnormalities of the immune system [15]. Most cases of autoimmune neutropenia are not associated with underlying disease and referred to as Chronic Benign Neutropenia (CBN). In children, this commonly occurs between ages of 5 and 15 months, but the range extends from 1 month to adulthood. The disease is characterized by the inability to increase WBC count when ill. The majority of pediatric cases will recover by adulthood without intervention. Antineutrophil antibodies are detected in 98–100% of patients with autoimmune neutropenia. Diagnosis can be assumed if a patient has isolated neutropenia, no dysmorphic features, no hepatosplenomegaly, no bone pain, no chronic diarrhea, no severe or unusual infections, and no other signs of significant underlying disorders. Treatment of the neutropenia is not typically required as it is usually mild and not associated with severe infections [19].

Chronic Idiopathic Neutropenia

Chronic idiopathic neutropenia (CIN), also known as benign chronic neutropenia, is a term which describes patients with chronic neutropenia for which there is no underlying cause. This condition tends to occur in late childhood or adulthood and does not usually undergo spontaneous remission. The ANC ranges from 500 to 1000/μL and often accompanied by monocytosis. The clinical course is typically benign despite the degree of neutropenia, possibly because there is usually marrow reserve. Treatment directed at increasing the neutrophil count should be reserved for those with significant and recurrent infectious complications.

Alloimmune (Isoimmune Neutropenia)

The incidence of alloimmune neutropenia has been estimated at 2 per 1000 live births. The neutropenia occurs due to transplacental passage of maternal IgG antibodies to neutrophil specific antigens inherited from the father. The pathogenesis is similar to that of Rh hemolytic disease. Infants may present with sepsis or be asymptomatic. It may be difficult to discern if the sepsis was caused by neutropenia or if the neutropenia is a result of sepsis. Antinuclear antibodies can be detected in infant and maternal serum and may show specificity for father's neutrophils. This is typically noted in an otherwise normal infant and the course is usually benign. Neutropenia resolves within 12–15 weeks although prolonged cases have occurred. If necessary, infants who are severely septic may be treated with G-CSF and complete evaluation can occur after the course of illness to determine if the neutropenia is alloimmune or a subtype of congenital neutropenia.

Nutritional Neutropenia

Neutropenia may be caused by deficiencies in vitamin B12, folate and copper, all of which are common in those who abuse alcohol. The neutropenia will typically resolve with appropriate supplementation of the deficient vitamins but may take 2–4 weeks to resolve. Deficiencies of folate and B12 may also result in a concomitant macrocytic anemia.

Other Hematologic Disorders

Hemochromatosis

Hereditary hemochromatosis (HH) is an autosomal recessive inherited disorder with low penetrance, meaning that biallelic mutations are usually required for clinically significant disease but many individuals with biallelic mutations will

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Table 2 Screening thresholds for Hereditary Hemochromatosis molecular and genetic testing

	TSAT (transferrin saturation)	Ferritin
British Society for Hematology (2018)	>40% for women and >50% for men	>300 ng/mL (>300 mcg/L) for men or >200 ng/mL (>300 mcg/L) for women
American Association for the Study of Liver Disease (2011)	>45%	>200 ng/mL for men and >150 ng/mL for women or above the upper limit of normal for the testing laboratory
American College of Physicians (2005)	>55%	>300 ng/mL (>300 mcg/L) for men or >200 ng/mL (>300 mcg/L) for women

not be affected [20]. It is considered one of the most common genetic disorders in Caucasians in the United States and Europe. Mutations in the HFE gene are seen in most individuals with HH. The two common mutations include the C282Y allele and the H63D allele. Homozygosity for C282Y accounts for 90% of HH cases and is more commonly associated with clinical disease. The likelihood of clinically significant iron overload resulting in organ damage is most common in homozygous C282Y/C282Y, resulting in 10% of patients or higher. Compound heterozygous C282Y/H63D and homozygous H63D/H63D have significantly less propensity to iron-overload states. Clinical manifestations of HH typically occur after age 40 in males and even later in females due to blood loss from menstruation. Symptoms generally occur after decades of organ iron deposition and total body accumulation as high as 20 g. These symptoms may include cardiomyopathy, dysrhythmias, cirrhosis, hepatocellular carcinoma, bronzing of the skin, diabetes, arthralgias, generalized cognitive impairment, secondary hypothyroidism, susceptibility to certain infections, osteoporosis and hypogonadism. Routine availability of iron studies and identification of the HFE gene have converted the typical presentation of HH from end-stage disease to a laboratory diagnosis typically made in asymptomatic individuals.

There should be a low threshold to perform laboratory testing if the diagnosis is suspected. This may be the case in individuals with unexplained fatigue, clinical symptoms of iron overload, porphyria cutanea tarda, a first- or second-degree relative diagnosed with HH or found to have an HFE mutation or the following laboratory test results: unexplained liver function test abnormalities, high serum ferritin (>300 ng/ml in men or postmenopausal women; >200 ng/ml in premenopausal women), high transferrin saturation (TSAT; >45% for men or >55% for women) or the HFE gene mutation. Iron studies are the initial test used to determine whether there is clinical evidence of iron overload. Routine studies include serum iron, serum transferrin (also reported as total iron-binding capacity), TSAT, and serum ferritin level. There are varying values that are considered concerning for excess iron stores depending on the institution's guidelines. The table below details the thresholds for the British Society for Hematology, the American Association for the Study of Liver Disease and the American College of Physicians (Table 2).

Diagnosis is made in an individual with iron overload and homozygous or compound heterozygous HFE mutations. Diagnosis based on laboratory values may be challenging due to ferritin being an acute phase reactant as well as the iron storage protein. If there is any question about interpretation of high ferritin level/presence of excess iron deposition, MRI should be used to further assess. MRI of the liver should be performed in individuals with elevated LFTs, hepatomegaly or clinical findings suggestive of cirrhosis, or ferritin >1000 ng/mL. Cardiac MRI should be performed in individuals with signs of heart failure on history or echocardiography, unexplained conduction abnormalities on electrocardiography, or significant liver iron deposition. Liver biopsy is not required for the diagnosis for HH and has been replaced by MRI for estimation of iron stores in the majority of patients. It may be useful, however, to obtain information regarding the extent of fibrosis, presence of cirrhosis, and ruling out alternative causes of advanced liver disease.

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Treatment should include regular phlebotomy (typically start at once-weekly sessions) to reduce the amount of circulating iron. The amount of phlebotomy needed to maintain appropriate circulating iron varies by patient and degree of overload. The degree of response is typically assessed by the serum ferritin level. Some guidelines (AASLD) target a ferritin level in the normal range, which is variably defined as 50 ng/mL, 30–100 ng/mL, or 50–150 ng/mL. Other guidelines (BSH) use a target ferritin level in the low-normal or iron-deficient range of approximately 5–10 ng/mL or 20–30 ng/mL. Individuals with advanced hepatic fibrosis are at risk for development of hepatocellular carcinoma and should have surveillance as per guidelines for any cirrhotic patient, including biannual ultrasonography or biannual AFP levels.

Polycythemia

Polycythemia Vera is one of the chronic myeloproliferative neoplasms which is distinguished clinically from other MPNs by the presence of an elevated red blood cell mass, although this alone is insufficient to make the diagnosis [21]. The 2016 World Health Organization Major criteria for diagnosis is as follows: Hemoglobin >16.5 g/dL in men or >16.0 g/dL in women, hematocrit >49% in men or >48% in women, or other evidence of increased red cell volume, bone marrow biopsy showing hypercellularity for age with trilineage growth including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes, and JAK2 V617F or JAK2 exon 12 mutation. Minor criteria include serum erythropoietin level below the reference range for normal. Diagnosis is made when all three major criteria are met or when two major and one minor criteria is met. PV occurs in all populations and in all ages, with median age at diagnosis being approximately 60 years. Incidence is slightly higher in men than women (2.8 vs. 1.3 cases/100,000 per year). Most patients are discovered incidentally with elevated hemoglobin or hematocrit found on routine blood work. Classic clinical symptoms of patients with PV include headache, dizziness, visual disturbances, pruritus, erythromelalgia (burning pain in hands or feet accompanied by erythema, pallor, or cyanosis), early satiety, splenomegaly, and vasomotor symptoms [22]. Aquagenic pruritus is often the chief complaint in patients with PV, characterized by pruritus following a warm bath or shower.

The goals of treatment are to reduce the risk of thrombosis, prevent bleeding events, alleviate symptom burden, and minimize the risk of evolution to other myelodysplastic syndromes. Patients are categorized as high risk or low risk based on age (<60 years old vs. >60 years old) and history of prior thrombosis. Low-risk patients (those less than 60 and with no history of thrombosis) may be treated with serial phlebotomy to maintain HCT <45% in men and <42% in women, low-dose aspirin, and optimal medical management of cardiovascular risk factors. High-risk patients (those older than 60 years old or have a history of thrombosis) should be treated with phlebotomy, low-dose aspirin, cytoreductive therapy with hydroxyurea (interferon alfa or busulfan may be used as alternatives), treatment of symptoms, and assessment of cardiovascular risk factors.

Secondary polycythemia can arise from underlying lung or heart disease, living at high altitudes, or smoking. If hypoxia is associated with lung or heart disease, RBC counts should improve with the addition of supplemental oxygen.

Sickle-Cell Disease

Sickle-Cell Disease (SCD) is an autosomal recessive inherited disease caused by a defect in the beta chain of the normal hemoglobin molecule, hemoglobin A, resulting in sickle hemoglobin molecule, hemoglobin S [23]. Hemoglobin S is less soluble than hemoglobin A and when it is deoxygenated, it becomes dysfunctional. Those who are homozygous for the sickle-cell gene have sickle-cell anemia (Hb SS), while those who are heterozygous have sickle-cell trait (Hb S trait). The clinical manifestations of SCD are related to hemolytic anemia and vaso-occlusion, which may lead to acute/chronic pain,

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as well as tissue ischemia or infarction. Splenic infarction leads to functional hyposplenism early which predisposes these patients to infection. Sickle-cell disease affects 70,000–100,000 people in the United States, of predominantly African and Hispanic descent.

The morbidity and mortality associated with sickle-cell disease primarily stems from complications of chronic hemolysis, tissue infarction, and acute pain crises. The vaso-occlusion results from the reduction in deformability, increased adhesion to vascular endothelial cells, inflammation, and activation of hemostatic mechanisms. This typically results in severe pain, which may be superimposed on underlying chronic pain. Pain may be accompanied by tissue ischemia and inflammation. There are certain triggers such as cold temperatures, wind, low humidity, dehydration, stress, alcohol, and menses. Over 90% of patients will have experienced a pain crisis by the age of 6. Patients with Hb SS have significant clinical manifestations compared to Hb S trait patients who typically are asymptomatic.

Sickle-cell patients are susceptible to infection due to functional asplenia that develops early in life, but preventive measures including vaccination (particularly against pneumococcal organisms) and prophylactic penicillin (from age 2 months to 5 years) have decreased the mortality associated with these infections. Administration of both the conjugate (PCV13) and polysaccharide (PPSV23) pneumococcal vaccine provides protection at the earliest possible age and broadens protection against most of the invasive pneumococcal serotypes. A fever should be considered a medical emergency and should prompt evaluation by a healthcare provider, blood cultures, and broad-spectrum antibiotics.

Acute manifestations of SCD include painful crises, acute chest syndrome (ACS), and multi-organ failure syndrome. Pain crises should be managed with opiates, and patient-controlled analgesia should be considered in those that are difficult to manage. Ketorolac may be used adjunctively. Oxygen supplementation should be reserved for patients who are hypoxic and incentive spirometry should be used to prevent the progression to acute chest syndrome. Acute chest syndrome typically presents with shortness of breath, cough, chest pain, fever, and infiltrate on chest x-ray. Antibiotics should be administered when fever or infection is present. Hydration with hypotonic fluids is indicated after appropriate volume resuscitation. Multi-organ failure may manifest with rhabdomyolysis, altered mental status, decreased urine output, worsening anemia, and decreasing platelet counts. Preventative measures include prophylactic antibiotics and immunizations, hydroxyurea, and transfusions. Stem cell transplant may be indicated in young patients with multiple sickle-cell disease-related complications.

Red blood cell transfusion should be reserved for clinical scenarios in which they may reduce morbidity, including stroke prevention, reduction of acute chest syndrome and pain crises, given that the pain is occurring in the setting of severe anemia. Other transfusion indications include acute multi-organ failure, acute symptomatic anemia, a drop in baseline reticulocyte count, and hepatic or splenic sequestration. Prophylactic transfusion should be considered preoperatively to achieve a hemoglobin level of 10 g/dL to reduce complications. Side effects of recurrent transfusion include iron overload which may be treated with deferoxamine. Routine transfusions carry the same risk as in the normal population, including acute transfusion reactions and delayed hemolytic reactions.

There are significant psychosocial factors associated with sickle-cell disease, including the management of chronic pain which may be stigmatized. This may cause patient's significant psychological distress, caregiver burnout, and/or secondary gain. It is imperative for physicians to take into account these factors when caring for patients with chronic and undertreated pain. Families of patients should also be educated extensively on the course of this disease and how to manage the complications that may arise.

Hematologic Malignancies

Multiple Myeloma

Multiple myeloma (MM) is the most common bone malignancy characterized by the neoplastic proliferation of plasma cells producing a monoclonal

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immunoglobulin, or M proteins (IgG, IgM, or IgA or rarely IgE or IgD). These clonal plasma cells proliferate in the bone marrow and can cause skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures [24]. The number of new cases diagnosed in the U.S. is 4–5 per 100,000 men and women per year [25]. Median age at diagnosis is66 years old, and incidence increases with age [26]. The diagnosis is more common among males than females (approximately 1.4:1) and two to three times more common in African Americans than Caucasians [24]. Clinical symptoms include bone pain, malaise/generalized weakness, weight loss, anemia, recurrent infections, renal insufficiency, and hypercalcemia. As routine blood work has become more common, patients are being diagnosed earlier in the disease course. Initial workup when diagnosis is suspected includes CBC, CMP, ESR, and serum and urine protein electrophoresis in addition to cross-sectional imaging. MM is sometimes suspected based on an increased serum protein level along with signs and symptoms that suggest myeloma. However, patients with light chain myeloma may have a normal total serum protein level as the free light chains may not rise to a level that affects total protein [24].

Among patients with MM, 97% will have a monoclonal M protein produced and secreted by plasma cells. This can be detected by protein electrophoresis of the serum (SPEP), or an aliquot of urine (UPEP) from a 24-h collection, combined with immunofixation of the serum and urine [26], in addition to end-organ impairment (hypercalcemia, renal insufficiency/elevated creatinine, anemia, and bone lesions). Peripheral smear will most frequently show rouleaux formation (>50%), where red blood cells take on the appearance of a stack of coins, leukopenia (20%), or thrombocytopenia (5%) [26].Cross-sectional imaging is preferred for diagnosing myeloma for the increased sensitivity in detecting bone involvement compared to plain radiographs [24]. A whole-body low dose CT is used initially as a baseline assessment for bone involvement; if these results are inconclusive and MM is the leading diagnostic differential, a whole-body MRI, or MRI of spine and pelvis is used to confirm the absence of bone lesions as MRI is more sensitive in detecting focal bone marrow lesions. MRI is also preferred if there is a concern for spinal cord compression or soft tissue plasmacytomas. PET/CT is used to detect extramedullary disease outside the spine.

The diagnosis of MM requires biopsy-proven bony or soft tissue plasmacytoma, or clonal bone marrow plasma cells greater than or equal to 10% estimated by a core biopsy specimen or aspirate, plus either the presence of end-organ damage or a biomarker indicating inevitable progression to end-organ damage (i.e. greater than or equal to 60% clonal plasma cells in the bone marrow) [24].

A premalignant disorder known as monoclonal gammopathy of undetermined significance (MGUS) carries a risk of progressing to MM at about 1% per year. The criteria of diagnosing MM include <10% of clonal bone marrow plasma cells, the absence of end-organ damage, and serum M protein <3 g/dL [24]. Waldenstrom macroglobulinemia is demonstrated by lymphoplasmacytic lymphoma in the bone marrow and IgM monoclonal gammopathy in the blood.

All patients with symptomatic MM are evaluated for hematopoietic stem cell transplant (HCT) eligibility, which can prolong overall survival compared to chemotherapy alone [26]. Bisphosphates should be prescribed to prevent vertebral fractures, as well as opiates for bone pain management. Vertebral compression fractures can benefit from percutaneous vertebroplasty and kyphoplasty for stabilization. Almost all patients will eventually relapse after initial treatment and will require additional therapy in the form of HCT or chemotherapy [26].

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a group of malignant disorders involving hematopoietic stem cells that lead to dysplastic and ineffective production of red blood cells (RBC), platelets, and mature granulocytes, with a risk of progression to acute leukemia [27]. The defects of RBC, platelets, and neutrophils can result in symptomatic anemia (most common), bleeding, and increased risk of infection, respectively. Approximately 10,000 cases are diagnosed annually in the U.S, although this is likely an underestimate as patients

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with early, nonspecific symptoms may evade testing due to comorbidities. The median age of diagnosis is 65 years, with a male predominance [28]. The age-adjusted 3-year survival rate for MDS is approximately 60%. Environmental factors (including exposure to benzene, radiation, or chemotherapy), genetic abnormalities (Fanconi anemia, trisomy 21, Bloom syndrome, ataxia telangiectasias), and benign hematologic disorders (paroxysmal nocturnal hemoglobinuria, congenital neutropenia) can predispose one to develop MDS [27].

Signs and symptoms of MDS are nonspecific, and many patients at presentation are asymptomatic or may present with fatigue or infection from a previously unrecognized cytopenia (ref2). MDS is commonly diagnosed based on anemia (hgb < 10 g/dL), neutropenia (absolute neutrophil count <1.8109/L), and thrombocytopenia (<100 109/L) (ref1). Peripheral blood smears usually reveal dysplasia in the red and white blood cell lines, whereas platelets are morphologically normal (ref1). Bone marrow aspirate will reveal a shift towards more immature precursors, with a blast percentage of less than 20% on aspirate as well as peripheral blood indicating MDS (ref2). Bone marrow biopsy will reveal specific histological features associated with MDS (fibrosis) and can help determine the stage of MDS [28].

Immediate treatment is warranted for those with symptomatic anemia, recurrent episodes of bleeding, or recurrent infections secondary to neutropenia [28]. Treatment of asymptomatic patients does not improve long-term survival, but these patients can be monitored with serial lab work. Allogeneic hematopoietic cell transplantation is the only cure.

Therapy including hematopoietic growth factors and immunosuppressive therapy can improve quality of life but are not curative. Chemotherapy can quickly improve blood counts and alter the disease course, reducing the risk of death [28].

Leukemias

Leukemias are a group of blood cell cancers that result from uncontrolled clonal proliferation of hematopoietic stem cells in the bone marrow [29]. These cells disrupt the normal expansion of blood cells causing symptoms such as weakness, infection, bleeding, and other complications [29]. Classification of leukemias is based on acute versus chronic, and lymphoblastic versus myelogenous.

The age-adjusted incidence rate of leukemia within the United States was 14.1 per 100,000 persons between 2012 and 2016 (for all races and both sexes) [30]. Roughly 1.6% of people will develop leukemia in their lifetime based on data from 2014–2016. Disease incidence increases with age with the median age of diagnosis around 65 years, and white males have a higher predominance than females or other ethnicities [30].

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer accounting for about 25% of childhood malignancies, and acute myelogenous leukemia (AML) accounts for 80% of acute leukemias in adults [29]. Chronic lymphocytic leukemia (CLL) occurs most commonly in people over the age of 50 and affects males more often than females. Chronic myelogenous leukemia (CML) accounts for 20% of all adult leukemias, with median age of diagnosis at age 65.

Predisposing risk factors include genetic abnormalities (Down syndrome, Neurofibromatosis, Fanconi anemia), genetic familial mutations, exposure to ionizing radiation, industrial chemical exposure (benzene), myelodysplastic syndrome, and prior chemotherapy or radiation therapy.

Common presenting signs of leukemia in children are persistent fever, anorexia, pallor, fatigue, abnormal bleeding or bruising, or petechial rash [31]. Hepatosplenomegaly is also a common finding and is a manifestation of anorexia or abdominal pain. Patients with lymphadenopathy unresponsive to antibiotics should be evaluated for ALL. One-third of all children can have bone pain that is usually presented with a limp or inability to weight bear. Priapism is a red flag for childhood leukemia. Adults will have the common presenting signs detailed above in addition to weight loss and anemia-related symptoms such as dyspnea or chest pain. Palpable lymphadenopathy and organomegaly are not as common in adults.

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If diagnosis is suspected, an initial CBC and differential is drawn which, at presentation, may show normocytic, normochromic anemia, thrombocytopenia, but a varying leukocyte count with about 25–40% of patients having less than 5000 cells/μL, and 20% of patients having a count above 100,000 cells/μL. Reticulocyte count will be normal or decreased [32]. A complete metabolic panel and coagulation panel may be assessed for any concurrent abnormalities and will give the hematologist/oncologist baseline liver functions.

Hyperphosphatemia, hypocalcemia, hyperuricemia, and/or hyperkalemia is indicative of tumor lysis syndrome and is an oncologic emergency [33]. A peripheral smear and bone marrow exam are required to detect characteristic morphology and immunophenotypic of cells for diagnosis. Excisional or needle core biopsy is pertinent to evaluate any suspicious lymph node. Any positive lab findings in light of symptoms require prompt referral to a hematology/oncology specialist.

The optimal treatment for children with ALL is a multidrug regimen with a protocol taking up to 3 years to complete [32]. Most patients require transfusion support at the time of diagnosis as well as antibiotic therapy. Rarely, exchange transfusion may be required in cases of extreme leukocytosis. Treatment for AML is based on medical fitness, prognostic features of cytology, and goals of care [33]. Chemotherapy is the mainstay of treatment, and supportive care includes transfusions and antibiotics as needed. Treatment for CLL is indicated if the patient has certain disease-related complications, including progressive bone marrow failure indicated by worsening anemia/thrombocytopenia, extranodal involvement, splenomegaly extending to greater than or equal to 6 cm below the costal margin, lymphadenopathy greater than or equal to 10 cm in length, constitutional symptoms, or progressive lymphocytosis because patients with CLL without treatment can have survival rates comparable to the normal population [34]. Treatment options for patients with CML include tyrosine kinase inhibitors, allogeneic hematopoietic stem-cell transplantation, or cytotoxic agents.

As more and more children with leukemia are surviving postchemotherapy, it is important for the family physician to provide routine care for these patients. In addition to any age-appropriate USPSTF cancer screening guidelines, a leukemia survivor should have follow-up with oncology every month for the first year after completion of therapy, then less frequently for the next 2–4 years, with yearly follow-up being appropriate after 3–5 years [32]. The primary care physician should be vigilant in regards to relapse with symptom monitoring, which are similar to those at initial presentation, as well as paying close attention to abnormal blood counts at follow-up, as 2–3% of ALL survivors can develop a second malignancy and many are at risk of developing a primary brain tumor [35]. Long-term effects of leukemia and its treatment are becoming more common as more patients survive these cancers.

Late adverse effects include CNS impairment, impaired linear growth, cardiotoxicity, endocrinopathies, higher likelihood of a secondary cancer, neurocognitive dysfunction, and depression. There is additionally an increased risk of late-occurring stroke in survivors of ALL. A decline in cognitive function is a common finding, especially in patients who received cranial radiation or triple intrathecal chemotherapy. These patients should receive neuroimaging and intermittent cognitive testing. Endocrinopathies include gonadal dysfunction, thyroid disorders, obesity, and low-growth hormone levels, although "catch-up" growth can be attained after completing chemotherapy. Patients that have been treated with anthrayclines (such as doxorubicin) need to be monitored for cardiotoxicity, including fatal cardiomyopathy. Since high-dose steroids are often used with chemotherapeutic regimens, monitoring for osteonecrosis of joints and osteoporosis must be undertaken. All patients having had a hematopoietic stem-cell transplant must have an initial bone scan 1 year after transplantation and then serially repeated based on clinical picture [35].

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Part XXVI

Family Medicine Applications

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Medical Informatics, the Internet, and Telemedicine

132

Michael D. Hagen

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History of Medical Informatics

General purpose electronic computers appeared in 1946 with the creation of ENIAC and were first theorized as potentially useful for medical diagnosis by Ledley and Lusted in the 1950s [1].

In the 1970s, Dr. Octo Barnett developed an electronic record system at Massachusetts General Hospital using a computer language (MUMPS) created for the purpose [2]. The term "medical informatics" appears to have arisen in France in the 1960s ("Informatique Medicale") [3] and came into common use in the 1980s as the preferred terminology to describe information technology applications in healthcare [4].

Healthcare applications exploded with the development of the World Wide Web by Tim Berners-Lee in the early 1990s, which enabled the development of information exchanges, online libraries and healthcare computer applications [2]. As health informatics applications became more prevalent, informatics practitioners began to form organizations to support their professional

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efforts. The first annual meeting of the Symposium on Computer Applications in Medical Care (SCAMC) occurred in 1977 and included tutorials on computer technology as well as presentations regarding use of computers in diagnosis and decision-making and laboratory analyses [5]. SCAMC ultimately evolved into the American Medical Informatics Association (AMIA), which continues to serve as a convening organization for informaticists of all disciplines and supports efforts in the following missions: Translational Informatics, Clinical Research Informatics, Clinical Informatics, Consumer Health Informatics, and Public Health Informatics [6].

The American Board of Medical Specialties (ABMS) approved Clinical Informatics as a new subspecialty sponsored by the American Board of Preventive Medicine and the American Board of Pathology. In creating the specialty, AMIA defined the content and a proposed curriculum for clinical informatics training programs (the specialty approval included a practice-eligibility pathway that will expire at the end of 2022) [7–10].

The Role of Clinical Informaticists

So what roles do these board-certified clinical informaticists assume in their professional contexts? A recent survey of clinical informaticists identified five principal domains: fundamental knowledge and skills, improving care delivery and outcomes, enterprise information systems, data governance and data analytics, and leadership and professionalism [11]. According to this survey, respondents spent the largest percentage of their time, 32%, in the improving clinical care domain [11]. Leadership and professionalism consumed 26%; they spent 18% of their efforts in the Enterprise Information systems and data governance/analytics domains [11]. The authors of this survey indicated that evolution of the subspecialty, particularly in response to nearly universal use of electronic health records and the data they generate, has led to greater emphasis on data governance and analytics than identified in the original core content specification [8, 11].

Starting in 2023, clinical informatics certification will require formal fellowship training. As of this writing, 35 Accreditation Council for Graduate Medical Education (ACGME)-accredited training programs exist in primarily academic health centers across the country. AMIA maintains a listing of currently available training programs and their contact information [12]. Specific information regarding application for the Clinical Informatics Subspecialty certificate can be found at the American Board of Preventive Medicine website, https://www.theabpm.org/become-certified/subspecialties/clinical-informatics/ (note that pathologists must apply through the American Board of Pathology, https://www.abpath.org/index.php/taking-an-examination/subspecialty-certificate-examinations).

Artificial Intelligence (AI) and Machine Learning

Since the previous edition of this textbook, advances in computing power and access to greatly enhanced storage capacity (i.e., through cloud computing) have enabled AI and machine learning algorithms to assume a larger role in creating knowledge from vast quantities of information [13]. AI systems have found successful application in "data-intensive specialties like radiology, pathology, and ophthalmology" [14]. However, evidence for safety and effectiveness in actual patient care and outcomes remains elusive [15].

Early AI systems relied primarily on rule-based algorithms and tended not to function well when presented with information outside their intended range [15]. As noted, increasingly powerful computing technology and availability of large data repositories have promoted the use of statistical and computational reasoning methodologies (such as neural networks) not feasible just a few decades ago. These powerful technologies do, however, present new challenges in clinical application. For many of these systems, their "black

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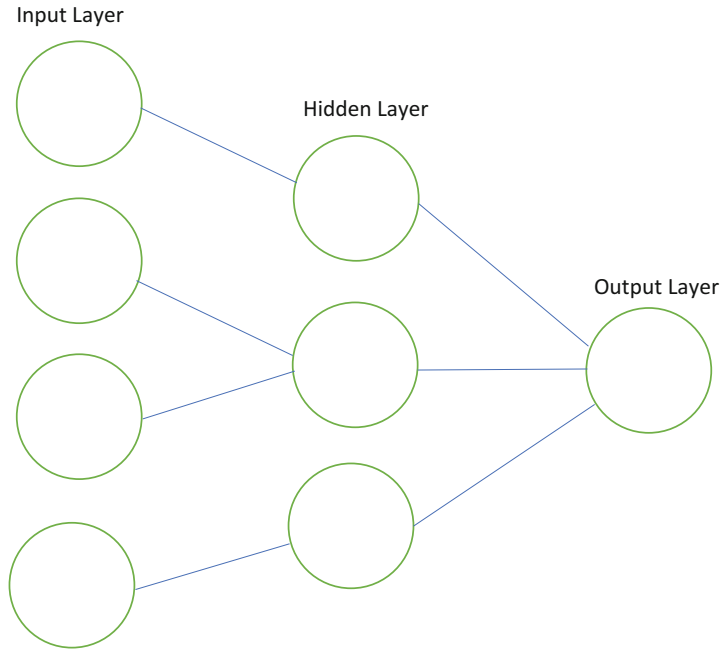


Fig. 1 Simple neural network with four input nodes, three hidden nodes, and a single output node. The input nodes represent the clinical characteristics the modeler wishes to use for predicting outcomes (e.g., demographics, clinical findings such as blood pressure). The hidden nodes evolve automatically as the network trains on a data training set. The output layer represents the outcome the modeler wishes to predict (e.g., mortality.) The lines between the nodes represent mathematical functions that change as the network trains. These functions serve as weights which combine mathematically with the node values to generate an output value. This output value compares to the true value; the difference generates a correction value that propagates back through the network iteratively until the network output values match the true values within a prespecified range

box" nature can present discomfort for patient and clinician alike if the developers haven't provided sufficient detail (such as the demographic and contextual characteristics of the data used to train the system, and problems identified in system creation) about the system's development, validation, and implementation [15]. Figure 1 displays a simple prototypical neural network. For those who might wish to explore machine learning techniques further, researchers at the University of Waikato in New Zealand have created an open-source platform (Weka) for learning about and using these tools [16]. This platform includes multiple machine learning methods (such as neural networks, Bayesian networks, linear regression, and others) and provides access to example datasets and tutorials that facilitate learning about these techniques.

Medical Informatics and Electronic Health/Medical Record Systems

The previous edition of this chapter included substantial information regarding vetting and selecting electronic health/medical record systems. Information from the Robert Graham Center for Policy Studies in Family Medicine indicates that at least 80% of new Family Medicine residency graduates enter employed positions after completing training [17]. This suggests that recent graduates will likely enter settings with already established information and electronic record systems (as of 2017 nearly 90% of office-based practices and 96% of non-federal hospitals had adopted electronic record systems [18]). Indeed, family physicians seeking employed status might

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want to consider characteristics of organizations' electronic information systems in their position decisions. A consensus statement from the American Academy of Family Physicians (AAFP), the American Board of Family Medicine (ABFM), the American Academy of Pediatrics (ABPeds), and the North American Primary Care Research Group (NAPCRG) examined functionality of existing electronic record systems and identified characteristics needed to enable electronic record systems to better support primary care: enhanced extraction, prioritization, and interpretation of information for individual patients and patient panels; advanced information exchange to support coordination, integration, and collaboration across providers and healthcare contexts (i.e., interoperability); greater facility for patient engagement; and reduced documentation burden [19].

The characteristic of interoperability remains a major challenge and shortcoming among currently available electronic medical record (EMR)/electronic health record (EHR) systems, particularly for small- and medium-sized practices [19]. The US federal government addressed interoperability in the twenty-first Century Cures Act [20]. The Act tasked the Office of the National Coordinator for Health Information Technology (ONCHIT) and the National Institute of Standards and Technology (NIST) to develop and promote standards "to ensure full network to network exchange of health information." [20] The ONCHIT released its final rule in March 2020 [21]. This rule establishes several requirements for electronic health records (EHRs): EHR providers must enable an individual patient's access to her data to qualify for EHR certification; providers must not block access to information (the rule does include exceptions for security and privacy); and EHR vendors have 3 years to bring their systems into compliance. Rather than have the vendors modify their proprietary data structures and interfaces to accomplish this interoperability, the ONCHIT has adopted the Health Level 7® (HL7) Fast Healthcare Interoperability Resources® (FHIR, pronounced "fire") standard for creating Application Programming Interfaces (APIs) to access individual products [22]. According to the rule, "this certification criterion will align industry efforts around FHIR Release 4 and advance interoperability of API-enabled 'read' services for single and multiple patients" [23]. Detailed discussion of the FHIR® standard is beyond the scope of this chapter, but suffice it to say that implementation of FHIR® promises to hasten access to disparate vendors' and systems' information for providers and patients alike.

Another technology related to FHIR and that can promote interoperability is the Substitutable Medical Applications and Reusable Technologies (SMART) specification [24]. SMART can be viewed as analogous to the apps developed for mobile devices. Using the SMART on FHIR approach, one can view the FHIR as the application programming interface (API) to a particular EHR product, while the SMART application serves as the app that performs a desired task (e.g., creating a graph) on the data extracted by the FHIR interface.

These interoperability developments should facilitate the progress of health information exchange (HIE). New payment models (e.g., value-based payment) and focus on patient-centered medical homes require coordination between multiple providers and organizations, and this coordination requires access to patients' data [25]. HIEs have demonstrated benefit in multiple outcomes: reduced hospital readmissions, reduced total costs, improved medication reconciliation, and improved immunization rates represent several of the benefits attained with effective HIE networks [25].

The Internet

The Internet developed as the Advanced Research Projects Agency Network (ARPANET) in the 1960s and served to support collaboration among defense researchers [26]. In 1983, ARPANET adopted the Transmission Control Protocol and Internet Protocol (TCP/IP) as the standard for data transmission, which enabled the Internet as a "network of networks" [26]. Subsequently, Tim Berners-Lee in 1990 created the components needed to enable the World Wide Web: hypertext transfer protocol (http), the universal resource

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identifier (URI), and the hypertext markup language (html) that enabled creation of web "pages" [27].

The World Wide Web (WWW) has provided clinicians access to myriad healthcare sites that provide medical decision support, access to the medical literature, and options for communicating directly with patients (e.g., through secure patient portals). (The large number of WWW citations in the reference list attest to the Web's impact on healthcare delivery!)

Clinical Decision Support

Numerous decision support resources exist on the Web, both subscription and open access. Several examples of subscription services include UpToDate® [28], DynaMed® [29], and Essential Evidence Plus® [30]. UpToDate® provides access to medical calculators, current medical management information and links to full-text articles, drug-drug interactions, and patient education. DynaMed® similarly provides calculators and specialty-specific (including Family Medicine) medical information. Essential Evidence Plus also provides calculators and evidence-based decision aids and adds access to Patient-Oriented Evidence that Matters (POEMs), Cochrane Systematic Reviews, and Evaluation and Management (E/M) coding support.

A number of open-access resources also provide valuable decision aids. The Mayo Clinic provides access to multiple sources for clinical guidelines (such as the American College of Physicians, United States Preventive Services Task Force, and the Centers for Disease Control and Prevention) [31]. Until recently, the Agency for Healthcare Research and Quality (AHRQ) supported the National Guidelines Clearinghouse, which provided access to clinical guidelines from multiple sources [32]. Funding has ended for this resource, but the ECRI Institute Guidelines Trust® now provides a similar tool [33]. The ECRI site does require a no-charge registration for access to the resources. Once registered, the user can browse/search for information by topic, specialty (interestingly they don't include Family Medicine in the specialty list!), care setting, or role.

Epocrates® (see https://www.epocrates.com/ for a detailed description of features) represents another point-of-care resource that includes drug information, clinical guidelines, formulary information, medical calculators, and information on multiple specialty topics. Epocrates® comes in both free and subscription versions and supports both online and smart device (e.g., iPad®, iPhone®, and Android®) access.

The National Institute for Health and Care Excellence (NICE) in the United Kingdom provides access to rigorously developed evidence-based guidelines [34]. Additionally each technology appraisal created by the NICE includes a cost-effectiveness analysis which serves as the basis for service coverage by the National Health Service (NHS) in the United Kingdom. For example, the NICE guidance for naltrexone-bupropion concludes that this treatment is not recommended for weight loss, based largely on a cost-effectiveness analysis that was "highly uncertain because of uncertainties in the modeling assumptions." The NHS concluded that "more certainty is needed" that this treatment would provide value in managing obesity in the United Kingdom.

The National Library of Medicin (NLM) in the United States has created and provides free access to multiple online resources for providers, patients, and researchers [35]. PubMed provides access to all of the peer-reviewed literature that the NLM has indexed and provides tools for facilitating search strategies. MedlinePlus provides patients access to useful health information; the Open-I Tool provides a means to search multimedia such as images. TOXNET enables searches for hazardous substances and chemicals. ClinicalTrials.gov includes a database of private and publicly funded research trials around the world [36].

The PubMed Clinical Queries tool represents a particularly useful resource for searchers who wish to fine-tune their literature searches [37]. Using this tool, searchers can limit their queries to specific literature categories, such as systematic reviews or original clinical studies. The tool includes filters that the user can utilize to further tweak the search. Additionally, the site includes tutorials and training materials to help users maximize their results. The NLM has recently introduced a new interface to the PubMed

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tool, which provides somewhat more streamlined access to these tools [38].

The World Wide Web also includes voluminous resources for patients, more than can be listed here. The American Academy of Family Physicians (AAFP) provides a large number of patient resources at https://familydoctor.org/. WebMD® provides another source of information for patients, including resources regarding drugs, illness symptoms, and finding a doctor [39]. The Mayo Clinic also makes available a site that provides patient-oriented information regarding diseases and conditions, as well as a "symptom checker" and first aid recommendations (available at: https://www.mayoclinic.org/diseases-conditions).

Generalized search engines, such as Google® (www.google.com) and Yahoo® (www.yahoo.com), also provide access to legions of health information. However, users should be aware that some authors have questioned the reliability of recommendations obtained using these tools [40, 41] and that concerns about authorship, conflict of interest, and quality of evidence may affect the quality of the information obtained [42].

Emerging Internet Technologies

Blockchain

Several emerging technologies hold promise for healthcare contexts. Blockchain represents one of those technologies. Blockchain is essentially a digital ledger that maintains a nearly tamper-proof history of transactions related to the information in a chain of events. The blockchains are maintained in series of computer networks; each new transaction or "block" gets added to an existing chain, and the result (or "blockchain") becomes "sealed" through cryptographic techniques. In the healthcare realm, the technology theoretically could facilitate patient access to electronic record data, in that blockchains could maintain a record of all the various systems in which their data reside. The actual health information would remain in the respective record systems, but the blockchain would maintain a permanent record of how to access those data (see: https://munkschool.utoronto.ca/mowatcentre/inside-the-black-blocks/).

Additionally, a blockchain-based system could facilitate professional credentialing (e.g., hospital privileging) by consolidating the record of a physician's educational, training. and certification history [43]. As of this writing, these remain potential blockchain applications.

The Internet of Things (IoT)

Multiple devices (appliances, monitors, sensors, etc.) increasingly include Internet access among their features. These devices promise to improve the quality of life for aging populations. Ambient Assisted Living devices (such as smart thermometers/thermostats that can automatically respond to extreme heat events) and fall detectors can help maintain frail patients in their homes and facilitate daily activities of living [44].

According to the International Electrotechnical Commission/Systems Committees, Active Assisted Living (AAL) "has been shown to increase general health and quality of life measures" (more details available at: https://www.iec.ch/dyn/www/f?p=103:186:16692527879311::::FSP_ORG_ID,FSP_LANG_ID:11827,25). Indeed, remote patient monitoring (RPM), defined as "the delivery of healthcare to patients outside conventional settings enabled by a technological application or device," promises to connect patients to providers and services from the comfort of their homes [45, 46]. As an example, monitoring an asthmatic for acute attacks can alert providers and facilities to the need for urgent services and intervention [47].

Telemedicine/Telehealth

As this chapter goes to press, the United States finds itself in the throes of the worldwide novel coronavirus pandemic. The pandemic has placed a strain on traditional patient-facing healthcare services, emphasizing the need for patient interactions that don't involve face-to-face visits with a provider. Enter telemedicine/telehealth.

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Just what is telemedicine/telehealth? The American Telemedicine Association (ATA) advocates using the term "telehealth" rather than "telemedicine" to indicate the broad nature of current applications. ATA defines telehealth as "technology-enabled health and care management and delivery systems that extend capacity and access" (available from: https://www.americantelemed.org/resource/why-telemedicine/). The landscape for telemedicine/telehealth has changed quite substantially since this textbook's previous edition, particularly for video interactions. The ATA defines several examples of telehealth approaches: "mobile health," which uses the Internet and/or cellular telephone network to provide health information and peer-peer interactions; "live videoconferencing" (in a synchronous mode) which can include live consultations between primary care physicians and sub-specialists regarding specific patient care issues; "store and forward" (in asynchronous mode), which can include forwarding and storing images, laboratory, and other patient information for later review (email represents an asynchronous store-and-forward process); and "remote patient monitoring" that can include devices that measure vital signs, blood glucose, blood pressure, and other clinical parameters for use in managing patients' healthcare needs in their home environments (details available at: https://www.americantelemed.org/resource/why-telemedicine/) (Table 1).

So what sorts of patient care scenarios best lend themselves to telehealth approaches? Table 2 identifies a number of potential candidates.

How does a practice or organization get started with telehealth? The American Health Information Management Association has created a comprehensive tool kit for guiding providers through the process [48]. The AHIMA tool kit identifies three fundamental steps: "assess and define," "develop and plan," and "implement and monitor" [48].

Let's look at these steps in further detail. The AHIMA guidance indicates that the "assess and define" step includes the following components: identify and document the need and rationale for a telemedicine/telehealth program; define the services the telehealth/telemedicine program will provide; define the delivery mechanisms for the program; perform an environmental scan to determine the need and payment options for the services; determine who will own the record/s created in delivering the services; define responsibility for changes to the services, release of information, and data breaches; and identify possible jurisdictional issues (e.g., licensure) if the service/s cross state lines [48]. The "develop and plan" includes the following: define a plan using all the information gleaned in Step 1; define the steps needed to create and deploy the identified services; estimate the work effort required to create and deploy the services; create a timeline for system development; identify staff needs for the development effort; and create a plan for monitoring and evaluating the program's progress [48]. Step 3, "implement and monitor" includes actual deployment of the plans developed in Step 2 and monitoring the results [48].

In developing and deploying the services, the provider needs to involve the program's potential stakeholders. Table 3 illustrates those stakeholders telehealth developers might wish to consider.

Table 1 Features that clinicians should investigate when encountering a new electronic health/medical record system (After Kennell et al. [51])

Features to look for in a modern EHR	
Capture of adverse events (e.g., medication errors)	Capture of medication list information
Support for Clinicians' Cognitive Processes (i.e., medical decision support)	Support for identifying and documenting patient preferences
Standardized data format (e.g., HL-7 or C-CDA[a])	Support for capturing patient-reported outcomes data
Support for genomic information	Support for identifying phenotypic information (e.g., specific physical characteristics)

[a]Consolidated Clinical Data Architecture. Description available at: https://www.healthit.gov/topic/standards-technology/consolidated-cda-overview

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Table 2 Patient care services particularly amenable to telehealth/telemedicine approaches. (After Texas Medical Association [52])

Services most amenable to telehealth approaches	
Acute, uncomplicated clinical conditions	Surgical follow-up
Review of laboratory results	Urgent care conditions
Mental health sessions	Coverage for after-hours needs
Medication management	Triage for the need for additional care
Follow-up of chronic care conditions	Nutrition consultation and services

Table 3 Stakeholders to consider in developing telehealth/telemedicine services. After Anderson et al. [48]

Potential telemedicine/telehealth stakeholders	
Organizational executives and leaders	Risk management
Providers (e.g., nurses and physicians)	Marketing
Organizational information technology/informatics representatives	Patient safety/QI leadership
Department heads	Patient representatives
Education and training personnel	Program consumers
Human resources representative/s	Regulatory and Compliance representatives

What about reimbursement for telehealth/telemedicine services? As of this writing, the US Department of Health and Human Services (HHS) has relaxed HIPAA-related regulations, and CMS has liberalized reimbursement policies for telehealth/telemedicine services. These changes might not persist beyond the passing of the coronavirus pandemic; family physicians should check with all of their payors regarding reimbursement and coding requirements for telehealth/telemedicine visits (see https://www.ama-assn.org/delivering-care/public-health/key-changes-made-telehealth-guidelines-boost-covid-19-care for more detail).

What equipment will a practice need for delivering telehealth/telemedicine services? This could be as simple as a telephone (note that many payors will not reimburse for telephone-only services); video "virtual visits" will require a computer with video camera and broadband Internet access or a smart device as described earlier. For best audio quality, the physician should consider using a headset with microphone for higher fidelity than usually afforded by built-in computer microphones. Under current circumstances, HHS has relaxed security requirements for virtual visits, which means that physicians can use free services such as Skype® and FaceTime®, and subscription services such as Zoom® and GoToMeeting®, to deliver these services (more detail available at: https://www.ama-assn.org/delivering-care/public-health/key-changes-made-telehealth-guidelines-boost-covid-19-care). Again, these requirements could change once the pandemic has receded.

Patient portals represent a secure, HIPAA-compliant option for patient-physician interaction. Through a patient portal, individuals can access EHR records such as recent doctor visits, hospital discharge summaries, immunizations, medication lists, and laboratory results (see https://www.healthit.gov/faq/what-patient-portal for more detail). Many organizations' portals also support direct secure email interactions between patient and physician, as well as prescription refill requests.

In providing direct clinical care via telemedicine/telehealth, physicians have ethical obligations to ensure that they provide accurate information and perform competently. This includes proficiency in managing the technology used and understanding possible limitations of the modality [49]. Telehealth/telemedicine isn't appropriate for circumstances that require in-person, "hands on" interaction with a patient (e.g., auscultating the lungs in a patient with cough and fever). Physicians delivering these services need to remain mindful of the need for patients' informed consent, including determining

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whether or not patients and/or their surrogates have proficiency with the technology used [49]. Likewise, clinicians must practice the same privacy and confidentiality policies that they would in a hospital or outpatient setting; patients should be apprised of the potential security issues associated with care delivered electronically (e.g., potential for "hacking" of personal health information). Additionally, clinicians must document the encounter either through their electronic health record or a written note to assure continuity of care and appropriate follow-up [49].

Individual healthcare organizations might have their own specific guidelines/protocols for conducting telemedicine/telehealth services. For example, the University of Kentucky healthcare system has created documentation guidelines for use in its ambulatory electronic health record (Allscripts®) (details available at: https://covid-19.ukhc.org/wp-content/uploads/sites/121/2020/03/Enterprise-Telehealth-Documentation-AEHR.pdf). The templates provided include recommendations for verifying patient identity, assuring that the patient resides in the state, authorizations and consent for telemedicine services, and instructions for creating customized macros.

Conclusion

In conclusion, biomedical/clinical informatics represents a dynamic and rapidly evolving discipline. The family physician can keep abreast of new developments by accessing several general clinically oriented resources. Hoyt and Hersh's *Health Informatics: Practical Guide* (seventh edition) represents a useful single resource and is endorsed by the American Medical Informatics Association [50]. The *Journal of the American Medical Informatics Association* (JAMIA) and *Applied Clinical Informatics* (ACI) Journal provide cutting edge informatics developments but do require subscriptions. Finally, ACI Open represents a relatively new open-access, free source of informatics information (available at https://www.thieme.com/books-main/clinical-informatics/product/4339-aci-open).

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Complementary and Alternative Medicine

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William Hay, Laurey Steinke, and Louisa Foster

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A family physician guided by evidence finds themselves in a difficult position regarding complementary and alternative medicine (CAM). There is little evidence for the efficacy of these methods, and sometimes no evidence for their safety. On the other hand, patients are likely to use them. In 2007, 38% of adults in the USA used some form of complementary or alternative medicine according to the CDC National Health Statistics Report #12 [1]. It is important for a physician to maintain a welcoming atmosphere, in which a patient is comfortable discussing any and all forms of CAM they might be using, so they may provide important information to the patient about the possible benefits, limitations and risks of these methods [2].

Biological Based Therapies

Supplements

Supplements are by far the most used CAM in the USA, with 17,7% of adults reporting the use of a non-vitamin supplement in 2012; if vitamins are included the number goes up to 52%. While patient's think of these as distinct from their prescription medications, it should be made clear that, just as with prescription medications, these entities can have side effects and drug interactions. Additional confusion can arise because many of these supplements are known by several names [3] (Table 1).

It is important to remember that dietary supplements do not require FDA approval before marketing and will only be withdrawn for the market if complaints are made [4]. The Dietary Supplement Health and Education Act of 1994 limited the FDA's ability to oversee supplements, and thus there is no guarantee of quality, safety, or effectiveness. Only products that make specific claims about disease treatments must be proven safe and effective for their intended use via clinical trials, thus most products on the market make vague claims, and so are not required to undergo testing. Even the claims made in advertising are not scrutinized by the FDA; rather they are investigated by the FTC, which regulates truth in advertising, only when complaints are made.

Adulteration of supplements, meaning they contain unauthorized FDA regulated pharmaceuticals, is a frequent problem and the most common reason for the FDA to recall these products. The most commonly adulterated classes include supplements marketed for weight-loss (diuretics and stimulants), bodybuilding (anabolic steroids) and "male enhancement" (sildenafil). Microbial and heavy metal contaminants have also been found

Table 1 Resources on supplements

Using Dietary Supplements; Wisely National Center for Complementary and Integrative Medicine (NCCIM)	https://www.nccih.nih.gov/health/using-dietary-supplements-wisely
Herbs at a glance (NCCIM)	https://www.nccih.nih.gov/health/herbsataglance
Office of Dietary Supplements	https://ods.od.nih.gov/
MedlinePlus	https://medlineplus.gov/druginformation.html
Cochrane library	https://www.cochranelibrary.com
Agency for Healthcare Research and Quality	https://www.ahrq.gov/topics/m.htm
FDA dietary supplement ingredient advisory list	https://www.fda.gov/food/dietary-supplement-products-ingredients/dietary-supplement-ingredient-advisory-list
National Institutes of Health, Office of Dietary Supplements (NIH ODS): health professionals	https://ods.od.nih.gov/HealthInformation/healthprofessional.aspx

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in a variety of supplements at levels unsafe for consumption [5]. In one study, 20% of 193 Ayurvedic medicines (a traditional health care system from India) tested, contained excessive levels of heavy metals [6]. This is also a frequent problem with imported traditional Chinese and Mexican herbs. Supplements have also been found to be to contain unlisted natural or synthetic ingredients, while others contained no DNA of the herbs listed on the label [5].

There are companies that independently evaluate products for quality (Fig. 1), certifying that products contain only the listed ingredients in the stated quantities and that they contain no contaminants or ingredients known to be unsafe. While these certifications do not indicate effectiveness or protect patients against issues such as drug interactions and side effects, this analysis does reduce the risk of using supplements and it is highly recommended to use products displaying the seals of these laboratories.

Multivitamins

Multivitamins, which can contain as many as two dozen vitamins and minerals, without standard dosages, are the most used of the supplements in the USA. While erroneously thought to be needed routinely, their use can lead to over supplementation when taken by those already consuming a nutrient-rich diet. There is evidence that use of a multivitamin/multimineral supplement is associated with an increase in total mortality [7]. Iron supplementation is the most detrimental, while calcium and Vitamin D supplementation were associated with decreased total mortality. The takeaway message seems to be that supplementation is only needed in response to identified deficiencies.

Megavitamin Therapy

Megavitamin therapy, defined as the use of vitamins at dose at many times the usually



Fig. 1 Product seals of companies that certify supplements

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recommended dosing, has not been proven an effective treatment for any condition except those involving malabsorption or vitamin metabolism issues. On the other hand, many vitamins, most famously pyridoxine, can cause toxicity when excessively dosed. Although some supplements contain such excessive doses, this issue arises more commonly in patient ingesting multiple supplements containing the same nutrient.

Probiotics

Ingesting various solutions of "beneficial" bacteria is currently a common practice and has been investigated for a number of conditions. Common organisms included are *Bacillus* spp., *Bifidobacterium* spp., *Clostridium butyricum*, *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., and *Streptococcus* spp., alone or in combination. Keep in mind that because one probiotic helps a condition, it doesn't mean another probiotic will have a similar effect.

Probiotics have been shown to assist pediatric patients with IBS [8]. These studies were short term, and stool-samples showed that the gut microbiome rapidly returned to its normal state after supplementation ceased, so this intervention may need to be long term. No clear evidence of benefit exists for adults. For the more serious IBD, there is a lack of randomized-controlled trials [9]. Probiotics also have a moderate effect when used to prevent and treat antibiotic associated diarrhea in children [10] and in the prevention of *Clostridium difficile*-associated diarrhea in adults and children [11]. Caution is indicated when using these agents in the severely debilitated and immunocompromised since adverse events have been reported [10]. There are reports of inclusion of bacteria other than those on the label [12], which can put those suffering from chronic disease or the immunocompromised at risk of infection.

Herbal Medicines

Safety and efficacy of herbal medicines will be dependent in a large part on the expertise of those gathering the plants. This process is not regulated and for the most part not standardized. The active ingredients will vary with the batch and are generally not measured. Also, the number of active compounds in an herbal medicine varies, and can be large, making drug interactions and side effects more likely. The top botanicals sold in the USA in 2011–2012 are included in Table 2, while Table 3 lists supplements that are particularly dangerous.

Diet-Based Therapies

While there are many dietary modifications overseen by nutritionists and dieticians that are appropriate treatments for disease (examples are ketodiets for epilepsy and diabetes) it must be noted that the most common comment in meta-analysis and reviews for diet-based therapies is "paucity of evidence." In addition to this, there is not long-term evidence regarding the possible health benefits or dangers of the numerous fad diets that circulate. Some of the most common dietary interventions are dealt with in more detail below.

All of these fad diets can result in short-term weight loss resulting from caloric restriction, but none produce better results long-term than calorie restriction.

FODMAP

The low-FODMAP diet restricts foods with highly fermentable oligo-, di-, and monosaccharides, and polyols -, which purportedly trigger and/or exacerbate IBS. Although a low FODMAP diet was found to have a favorable impact on abdominal pain, bloating and diarrhea [14] this diet is not clearly superior to conventional IBS diets. A low FODMAP diet, administered by a dietician, is recommended by the British Dietetic Association and the NIDDK for management of IBS.

Keto- and Paleo-Diets

Keto diets are low-carbohydrate and high-fat diets that are claimed to produce weight-loss and provide benefits against diabetes, epilepsy, cancer and Alzheimer disease. A ketogenic diet results in the metabolism of fat for energy, with production of ketosis. The Paleo (or paleolithic) diet

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Table 2 Common supplements [45]

Supplement	Suggested use	Evidence	Contraindications and side effects
Alfalfa	Lower LDL cholesterol and numerous other conditions	Insufficient evidence to rate benefit	Safe in dietary amounts, Interferes with warfarin and other medications
Black Elderberry	Colds and flu, pain relief	No evidence of benefit	Parts of the plant and unripe berries are stomach irritants
Bilberry (European blueberry, whortleberry, huckleberry)	Poor circulation, menstrual cramps, eyestrain, skin problems or diarrhea	No support for use to treat any condition	Interacts with warfarin
Cannabidiol (CBD)	Nausea and vomiting, chronic pain, epilepsy	Low-quality evidence for efficacy, currently under active study	Diarrhea, sleeplessness, or abnormal liver function. Interacts with many medications including warfarin [46]. Not legal (federal)
Cranberry	Prevent or treat UTI	Some low-quality evidence of decreased risk of UTI. Not effective at treating UTI	In large amounts may cause stomach upset and diarrhea. May interact with warfarin
Echinacea (purple coneflower, coneflower, American coneflower)	Common cold	Does not decrease the length of the common cold, low-quality evidence it may reduce occurrence of colds	Digestive upsets, possibility of allergies, interacts with warfarin and other medications
Evening Primrose oil (EPO)	Eczema, rheumatoid arthritis, premenstrual syndrome, breast pain, and menopause symptoms	No evidence of efficacy	Digestive upsets, complications of pregnancy, interacts with warfarin to increase bleeding
Garlic	Lower cholesterol, prevent cancer, hypertension	Conflicting and weak evidence for all claims	Digestive upsets, interacts with warfarin and other medications
Ginger	Nausea	Moderate evidence of efficacy	Safe as a spice. Caution with large doses in pregnancy and with gallstones. Large doses can interact with warfarin, antihyperglycemics and other medications
Gingko biloba (fossil tree, maidenhair tree, Japanese silver apricot, baiguo, yinhsing)	Dementia, eye problems, intermittent claudication	No evidence that it is helpful for any condition	Seeds are poisonous. Possible increased liver and thyroid cancer risk, interacts with warfarin and other medications
Polyunsaturated fatty acids (Fish oil, Omega-3 Fatty acids)	Heart disease, high cholesterol, eye diseases, eczema, neurologic disorders	In statin treated patients, improves cardiovascular outcomes but not all-cause mortality [47]. All other conditions inconclusive or no benefit	Generally considered safe, can interfere with coagulation. Do not use some forms if allergic to seafood
Saw Palmetto (American dwarf palm tree, cabbage palm)	Benign Prostate Hyperplasia, chronic pelvic pain, migraine, hair loss	No more effective than placebo for BPH, no evidence of efficacy other conditions	May be unsafe during pregnancy or while breastfeeding
Soy	Menopausal symptoms, bone health, improving	Small effect on LDL when replaces other proteins. Low quality evidence for small	Dietary amounts safe. Supplements may cause Endometrial hyperplasia.

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Table 2 (continued)

Supplement	Suggested use	Evidence	Contraindications and side effects
	memory, hypertension and hyperlipidemia,	effects on menopause. Other conditions, no evidence	Safety not established for those with or at risk for breast cancer
St. John's Wort (hypericum, Klamath weed, goatweed, Tipton's weed, rosin rose, chase-devil)	Depression, ADHD, menopausal symptoms, IBS,	Inconclusive data for depression, no positive data for any other conditions	Interacts with many medications in a severe and often life -threatening way
Tumeric/Curcumin	Arthritis, diabetes, digestive disorders, respiratory infections, allergies, liver disease, depression, and others	Low quality evidence with no clear benefits. Currently under active study	Safe used as a spice, large amounts may be unsafe for use during pregnancy or while breastfeeding
Zinc [48]	COVID-19, common cold, viral infections, immune support	Poor quality evidence for reduction in length of common cold	Large doses produce digestive upset or, over the long term, reduced immune function. Interferes with absorption of some antibiotics

attempts to replicate the diet of ancient hunter-gatherers. While not as restrictive as the keto diet, and mimicking mainstream nutritional advice about avoiding processed food, it eliminates dairy, which can result in low calcium intake.

Juicing and Detoxification Diets

Juicing and detoxification diets promote very low-calorie intake for a short period of time (two to 21 days). Diarrhea is a frequent side effect. Herbs in these mixtures can cause difficulties as previously discussed. Such severely restricted diets can increase cortisol levels and lead to rebound weight gain.

Intermittent Fasting Diets

Intermittent fasting diets involve fasting for 16–48 h, followed by a period of unrestricted eating.

Gluten-free Diets

While necessary for those with Celiac Disease (1% of the population), gluten-free diets are also suggested for a variety of conditions in the popular press, including mood disorders and autism. There are no high-quality studies in favor of treating any disorder, other than celiac disease, with a gluten-free diet. Nonceliac gluten sensitivity is considered to be common (1–6% of the population). Food challenge studies indicate that in half the cases where nonceliac gluten sensitivity is reported, the symptoms were not replicated. Once on a gluten-free diet, reintroduction of gluten can provoke bloating and gas until an equilibrium is reached in the gut bacteria, so determining the efficacy of a gluten-elimination trial is difficult There is no scientific evidence of general contribution to a healthier life-style or effect on weight-loss [14]. Additionally, gluten-free foods are approximately three-times more expensive and may lack nutrients added to enrichened grain products.

Mind-Body Medicine

This category includes practices that are based on the human mind, but that have an effect on the human body and physical health, such as meditation, prayer, and mental healing.

Deep Breathing

Deep breathing and breathing exercises are the second most commonly used CAM after supplements and are useful in focusing a patient's

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Table 3 Dangerous supplements [49, 50]

Supplement	Suggested uses	Toxicities
Aconite (helmet flower, monkshood, devil's helmet, and wolfsbane)	Fever, pain, cough, asthma	Nausea, vomiting, weakness, paralysis, breathing and heart problems, possibly death
Bitter Orange (aurantii fructus, Citrus aurantium, zhi shi)	Weight loss, nasal congestion, allergies	Fainting, heart-rhythm disorders, heart attack, stroke, death
Caffeine Powder (1,3,7-trimethylxanthine)	Improves attention, enhances athletic performance, weight loss	Seizures, heart arrhythmia, cardiac arrest, possibly death; particularly dangerous when combined with other stimulants
Chaparral (Creosote bush, greasewood, larrea divaricata, larrea tridentata, larreastat)	Weight loss, improves inflammation. Treating infections, skin rashes, cancer	Kidney problems, liver damage, possibly death
Colloidal Silver	COVID-19, sinus infections, pain, bacterial infection, daily health.	Argyria (bluish-gray discoloration of skin, usually permanent), interferes with absorption of thyroxine and some antibiotics
Coltsfoot (Coughwort, farfarae folium leaf, foalswort, tussilago farfara)	Cough, sore throat, laryngitis, bronchitis, asthma	Liver damage, possible carcinogen
Comfrey (Blackwort, bruisewort, slippery root, symphytum officinaleh)	Cough, heavy menstrual periods, stomach problems, chest pain; treats cancer	Liver damage, cancer, possibly death
Country Mallow (heartleaf, Sida cordifolia, silky white mallow)	Nasal congestion, allergies, asthma, weight loss, bronchitis.	Heart attack, heart arrhythmia, stroke, death.
Germander (Teucrium chamaedrys, viscidum)	Weight loss; alleviates fever, arthritis, gout, stomach problems	Liver damage, hepatitis, possibly death
Germanium	Pain, infections, glaucoma, liver problems, arthritis, osteoporosis, heart disease, HIV/AIDS, cancer.	Nephrotoxicity and death
Greater Celandine (Celandine, chelidonium majus, chelidonii herba)	Alleviates stomachache	Liver damage
Green Tea Extract Powder (Camellia sinensis and many others)	Weight loss	Dizziness, tinnitus, decreased iron absorption, and glaucoma; elevates blood pressure and heart rate; liver damage; possibly death
Kava kava (Ava pepper, piper methysticum)	Anxiety, insomnia, premenstrual symptoms, and stress	Hepatoxicity and liver failure [22], Parkinson's and depression, impairs driving, possibly death
Lobelia (Asthma weed, lobelia inflata, vomit wort, wild tobacco)	Respiratory problems, aids smoking cessation	Nausea, vomiting, diarrhea, tremors, rapid heartbeat, confusion, seizures, hypothermia, coma, possibly death
Methylsynephrine (Oxilofrine, p-hydroxyephedrine, oxyephedrine, 4-HMP)	Weight loss, increases energy, improves athletic performance	Causes heart rate and rhythm abnormalities, cardiac arrest; particularly risky when taken with other stimulants
Pennyroyal Oil (Hedeoma pulegioides, mentha pulegium)	Breathing problems, digestive disorders	Liver and kidney failure, nerve damage, convulsions, possibly death
Red Yeast Rice (Monascus purpureus)	Lowers LDL, prevents heart disease	Kidney, muscle and liver problems, hair loss; duplicates effect of statin drugs, increasing the risk of side effects
Usnic Acid (Beard moss, tree moss, usnea)	Weight loss, pain relief	Liver injury

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Table 3 (continued)

Supplement	Suggested uses	Toxicities
Yohimbine (Johimbi, pausinystalia yohimbe, corynanthe johimbi)	Treats low libido and erectile dysfunction, depression, obesity	Raises blood pressure; causes rapid heart rate, headaches, seizures, liver and kidney problems, heart problems, panic attacks, possibly death

attention on the process of inhalation and exhalation. For patients who suffer panic disorder and anxiety, this exercise gives a focus to the thought process. It can improve lung function and exercise capacity in lung disease, the symptoms of GERD, and speed post-anesthesia recovery.

Meditation

Drawing from Buddhist practices and philosophy, meditation promotes healing by helping patients cultivate mindfulness skills and helping them to change their relationship with their own experience. Meditation is the formal discipline used to develop mindfulness, through awareness of the breath, use of a mantra or a passage in a sacred text, loving-kindness meditation or compassion practices, among others. Contrary to popular belief, it is not an attempt to "empty one's mind," rather it is a skill-based means of redirecting watchful attention to one's own cognition and affective reactions, without engagement or judgment. Cultivating these practices helps patients to shift focus from unconscious, automatic patterns of thought to present moment, non-judgmental awareness. As a result, patients experience a host of physiological benefits, including greater affect regulation, an increased capacity to tolerate distress, and decreased sympathetic nervous system arousal [15]. Ongoing mindfulness training engenders the development of "equanimity," a nonreactive posture to life events.

The development of mindfulness skills has significant implications in primary care populations as it promotes increased treatment compliance and engagement in preventative health care behaviors, as well as decreased subjective experiences of pain, yielding less reliance on opioids and narcotic interventions [16]. It has also been shown to decrease relapse of major depression and substance abuse [17]. Furthermore, mindfulness skills have positive implications for the clinician as well as the patient, by improving patient-centered communication skills, and increasing the personal well-being of the physician [18].

The availability of mindfulness training through a multitude of venues such as meditation centers, yoga studios, gyms and churches, and online training, makes it an affordable and accessible alternative to patients who have limited resources. In cases where stigma exists around accessing mental health treatment, mindfulness can offer resiliency training, allowing isolated patients to become connected in like-minded, health promoting settings.

Yoga

Yoga can be traced back to early civilizations in India. It focuses on the following principles: proper breathing (pranayama), proper relaxation (savasana), proper exercise (asanas), meditation (dhyana), and proper diet (vegetarian). There are many different styles of yoga, and none of them have been found to be superior over the other. Yoga was introduced to the USA in the late nineteenth century, but its popularity has rapidly increased since the 1960s. Randomized controlled studies have only been done on Yoga for a limited number of conditions. Beneficial effects are supported for depression, anxiety, LBP (equal to physical therapy) [19], and asthma. It has a small but consistent effect on hypertension (similar to other exercises). There is limited evidence of effect on sleep in patient's receiving chemotherapy. Studies show no effect on menopausal symptoms [20]. Minor MSK injuries are not uncommon. Relative contraindications include

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hypermobility and osteoporosis or other conditions with increased fracture risk. Patients with severe cardiac conditions, a predisposition to syncope, and pregnant women should avoid hot yoga (Bikram).

Biofeedback

Biofeedback is a technique a patient can use to learn to control some of their body's functions by using electrical sensors that help them receive information about their body. This feedback is used to achieve physiologic changes, such as relaxing muscles or reducing heart rate, to obtain a desired result such as reducing anxiety or pain. There are two types of biofeedback: physiological biofeedback and biomechanical biofeedback. Most evidence of effectiveness is in the areas of musculoskeletal and neurologic rehabilitation, anxiety, depression, and sports performance. There is no evidence of effectiveness in hypertension.

Hypnosis

Hypnosis is defined as "a trance-like state that resembles sleep but is induced by a person whose suggestions are readily accepted by the subject" (Merriam-Webster Medical Dictionary). Hypnosis is used for chronic pain, mental distress, smoking cessation, and sexual dysfunction, as well as changing other habits. While it is sometimes considered part of standard medical practice, and numerous workshops and schools offering certification in hypnotherapy are available, there is at best low-quality evidence for its efficacy in treatment of chronic pain and adverse outcome data in trials and clinical interventions does not seem appropriately documented. Controls vary widely in trials. Some studies compare hypnosis to other psychological interventions, some to patients maintained on a waiting list, some provide education and still others include an attention-equivalent empathic intervention. For adults, a meta-analysis [21] found hypnosis moderately effective for chronic pain in fibromyalgia, Multiple Sclerosis, phantom limbs, cancer and disability. The results in general are encouraging but no more so than other psychological interventions such as autogenic training, guided imagery and progressive muscle relaxation. Hypnosis is somewhat effective in reducing mental distress, but not pain, in adults undergoing dental procedures. Repeated studies have failed to find hypnosis effective for smoking cessation. In children, hypnotherapy (including guided imagery) was found effective in children presenting with recurrent abdominal pain in studies lasting up to 5 years. Side effects are infrequently evaluated in hypnosis studies, but when documented, minor, usually transient, effects such as dizziness, panic attacks, drowsiness, confusion, headaches, and fear occur at high rates [22].

Manual Medicine

The philosophies of manual medicine involve therapies that consist of movement or manipulation of the body. When considered together they represent the second most common class of CAM.

Osteopathic Manipulation

Osteopathy was started in 1874 by Andrew Taylor Still, MD, DO. His term "osteopathy" was based on the hypothesis that the pathology of most conditions stems from the bones themselves. Though this theory proved not to be true, osteopathic manipulative techniques (OMT) are still a part of osteopathic practice, albeit in a much-reduced role, primarily for treatment of musculoskeletal conditions and pain. Using OMT, an osteopathic physician (DO) moves a patient's muscles and joints using techniques that include stretching, gentle pressure and resistance. Treatments most commonly involve the spine, but OMT is used all over the body; common areas include the pelvis, shoulders, knees, ribs, and the paranasal sinuses. Today, OMT is most commonly used by primary care physicians and a smaller group of DOs who practice it full time. Courses and curricula are available to teach MDs these techniques and

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principles. Many studies show the effectiveness of OMT in low back pain with additional evidence for other musculoskeletal issues such as shoulder and neck pain, and headaches. Studies of non-MSK problems are limited but specifically do not support OMT for respiratory conditions [23]. Contraindications include local infection, fracture, herniated vertebral disc, inflammatory arthritis of the spine, cauda equina syndrome, and cancer. Serious complications are rare.

Chiropractic Therapy

Chiropractic was founded in 1895 by DD Palmer, a 'magnetic healer'. The chiropractic health model posits that most illness arises from chiropractic vertebral subluxations – improper juxtaposition of the vertebrae - which interfere with the flow of energy, originally called "Innate Intelligence," down the spine, through the nerves and into the body. This is considered the cause of most bodily dysfunction and disease; as opposed to the medical model in which diseases are caused by germs or pathophysiology (e.g., cancer). Traditional chiropractic treatment involves "adjustments", which correct these subluxations allowing proper flow of energy and natural healing. Practitioners may additionally manipulate other parts of the musculoskeletal system. Many Chiropractors today also use other techniques, frequently alternative ones as described elsewhere in this chapter, which is controversial within the chiropractic community. Indeed, the use of routine X-rays and even the concept of the subluxation are currently sources of controversy in the Chiropractic community.

Chiropractors are the only alternative practitioners licensed in all USA and Canadian provinces. Many Chiropractors focus adjustments on musculoskeletal disorders, particularly those of the spine. Studies show effectiveness for low back pain and neck pain; its effectiveness in headaches is more mixed. Chiropractic treatment of non-musculoskeletal conditions is controversial, but most chiropractors and their professional organizations consider adjustments appropriate for a wide variety of problems, from otitis media, asthma, and gastrointestinal symptoms to HIV and ADHD. There are, however, no high-quality studies show efficacy of chiropractic adjustments for these or any other non-musculoskeletal condition [24].

Minor side effects, such as muscular soreness, are common, occurring in up to a quarter of patients. Rare severe complications include fracture, vertebral disc herniation and cervical artery dissection [25, 26]. Contraindications to chiropractic manipulation include conditions where bony structures are susceptible to trauma such as fractures, bone tumors, severe rheumatoid arthritis, and osteoporosis. Manipulation should also be avoided in patients with a progressive neurologic deficit and in those who have a deteriorating condition without a clear diagnosis. Pediatric chiropractic care remains controversial. Given the lack of any published studies showing the benefits of chiropractic treatment in pediatric patients and the documented reports of serious complications, the treatment of infants and children cannot be recommended.

Massage Therapy

Massage therapy involves manipulating the soft tissues of the body. Massage has been practiced in most cultures, both Eastern and Western, throughout human history, and was one of the earliest tools that people used to try to relieve pain. Swedish massage is the most commonly used technique in the USA, but deep tissue, hot stone, aromatherapy, sports, pregnancy, Thai, and Shiatsu methods are also widely used.

There is surprisingly little evidence of benefits in MSK disorders and low back pain other than very short-term improvements. In athletes, there is no evidence of performance enhancement but some evidence of small improvements in flexibility and duration of soreness. There is positive evidence of improvement of QOL in fibromyalgia patients. There is mixed evidence of improvement in constipation, post-operative pain and labor pain. In cancer patients there is mixed evidence of improvements in pain, anxiety and depression but there are no studies to show any effects on

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cancer progression. Massage is a common intervention in infant nurseries with some evidence of benefits in feeding, weight-gain and hyperbilirubinemia, but study interventions are highly variable and firm conclusions are elusive. There is no evidence of benefits in COPD, non-cancer related depression or pressure ulcers.

Alternative Medicine Systems

Alternative medical systems refer to an entire system of theory and practice that developed separately from conventional medicine.

Homeopathy

Created in 1796 by Samuel Hahnemann, homeopathy is based on the prescientific principle of "like treats like," the belief that a substance that causes symptoms of a disease in healthy people would cure similar symptoms in sick people; for example, the aconite plant, which increases the pulse and elevates the temperature, is used for fever. However, many of these substances are very toxic so Hahnemann diluted them, eventually concluding that the remedies became more effective with increasing dilution, now called the "law of infinitesimal doses." Homeopathic remedies are diluted with alcohol or water either 1:10 (noted as "X" or "D") or 1:100 ("C"). So, a 6X product has been diluted 1:10 six times. a dilution of 10^6. Potencies of 30C or lower are called low-potency remedies or medicines, and potencies of 200C or higher are considered high-potency medicines. However, modern chemistry informs us that by a 12C dilution there is only a 60% chance of a single molecule being present in a solution, a chance that drops nearly to zero with an additional 1:100 dilution. The lack of any of the original compound in most homeopathic remedies has led to the concept of "water memory,, according to which water "remembers" the substances mixed in it and transmits the effect of those substances when consumed – a theory incompatible with modern chemistry.

As of 2020, all 12 Cochrane reports involving homeopathy failed to document any effects. Five large meta-analyses of homeopathy reached the conclusion, after excluding methodologically inadequate trials and accounting for publication bias and likely random statistical variation, that homeopathy produced no statistically significant effect over placebo" [27]. While such dilute solutions would appear to pose no risk, in addition to the possible delay or avoidance of effective treatments for serious conditions and preventative care, contaminated and inadequately diluted product have resulted in illness and even death [28]. As of 2020, no homeopathic products have ever been approved by the FDA

Traditional Chinese Medicine (TCM)

Traditional Chinese Medicine is based on the concept of Qi (pronounced "chee"), believed to be a vital force forming part of any living entity and circulating through 12 primary and 8 accessory channels. These channels (also known as meridians) are described as having branches connected to bodily organs and functions. In this belief, if the flow of qi along these meridians is blocked or unbalanced, illness can occur. Another important concept in traditional Chinese medicine is the concept that all things, including the body, are composed of opposing forces called yin and yang. Traditional Chinese medicine doctors look at the balance of body, mind, and spirit to determine how to restore qi, the yin-yang balance, and good health.

Diagnosis in TCM is focused on the "Four pillars": Inspection, focusing on the face and particularly the tongue; Auscultation (of voice, breathing and cough) and Olfaction (attending to breath and body odors); Inquiry, focusing on the "seven inquiries" - chills and fever, perspiration, appetite, thirst and taste, defecation and urination, pain, sleep, and menses and leukorrhea; and Palpation of the body for tender "Ashi" points, of pulses with special attention to the wrist, and of the abdomen.

TCM therapies include: acupuncture, acupressure, Chinese herbs, cupping (uses warm air in

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glass jars to create suction), diet (foods being either yin or yang), massage (tui na), moxibustion (uses heated Chinese mugwort), and exercises (tai chi and qigong). Evaluation of effectiveness is made more difficult as the basis concepts of TCM are radically different from "Western" scientific medication. However, reviews of TCM have found little evidence of effectiveness, often due to the low quality of the available studies. In addition to safety concerns with TCM reviewed elsewhere in this article. concerns exist over the illegal trade and transport of endangered species including rhinoceroses and tigers, and the welfare of specially farmed animals including bears

Acupuncture

Acupuncture is an alternative practice that involves stimulation of superficial points on the body for a medical effect. This is generally done using needles but pressure, electricity, lasers, and even bee stings are alternatively used. In TCM, qi is felt to flow through the body along paths called meridians and stimulation at acupuncture points corrects or balances this flow. In TCM, acupuncture is frequently combined with other TCM techniques. In the United States and Europe, acupuncturists frequently practice Western Medical acupuncture, which links acupuncture to medical diagnoses and frequently rejects qi-based theories in favor of those involving nerve or endorphin stimulation. Western Medical acupuncture focuses primarily on the relief of pain and other somatic symptoms while TCM is considered applicable to a wide variety of conditions as diverse as pain, infertility, allergies, and cancer. Practitioners who seek to refer a patient for acupuncture should understand the philosophy and techniques used by the consultant.

While acupuncture is often viewed as homogeneous, in fact there are many different forms of acupuncture [29]. Even within traditional needle acupuncture there are many variations involving differences in types of needles, depth of insertion, insertion techniques, how the needles are manipulated and most significantly the location of acupoints. Additionally, a 2009 review found "considerable variation" in localization of acupoints among qualified medical "acupuncturists" [30].

Overall, the effectiveness of acupuncture in randomized controlled trials has been disappointing; moderate evidence of effectiveness was found for acupuncture on prostatitis and fibromyalgia pain (but not fatigue), but not for the vast majority of other indications studied, including asthma, smoking, autism, depression, osteoarthritis, and neuropathic pain. In most of these studies either true acupuncture did not prove more effective than sham acupuncture (often using toothpicks or placebos that don't puncture the skin) or were too low in quality to allow a conclusion of effectiveness [31]. Recent reviews of acupuncture for pain, the most common indication in the USA, are conflicting on its effectiveness [32, 33].

Although most patients will not experience any complications from acupuncture, adverse events are not rare. Discomfort is by far the most common side effect; however, serious side effects include syncope, pneumothorax, infection, subarachnoid hemorrhage, and, rarely, death.

Naturopathy

Naturopathy is "a system of alternative medicine based on the theory that diseases can be successfully treated or prevented without the use of drugs, by techniques such as control of diet, exercise, and massage." While the stated goal of naturopathy, "to treat the whole person," is laudable, and addressing the root causes of illness using stress-management, exercise, and lifestyle changes are all appropriate goals, studies of naturopathic treatments are generally lacking in rigor and appropriate controls [34]. It is difficult to include a double-blind randomized control for an intervention such as naturopathy, and individual counseling by nutritionist and exercise therapists is not normally used as a control. There are 13 trials described in the Cochrane Library, but no reviews. The Doctor of Naturopathic Medicine (ND) is a 4-year degree. The curriculum includes approximately 60% of the clinical hours required for a Doctorate in Medicine or Osteopathy, with principles of

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homeopathy and other types of alternative medical treatments comprising most of the academic training [35]. Only a small minority of NDs complete anything akin to a residency. Twenty-five jurisdictions within the United States offer licensure to NDs although scope of practice varies from state to state. While there are some NDs practicing evidence-based medicine, in general naturopathy is based on the principle of vitalism, the idea there is a unique "life force."

Energy Medicine

These techniques involve the manipulation and application of energy fields to the body. In addition to electromagnetic fields outside of the body, it is hypothesized that energy fields exist within the body. The existence of these biofields has not been experimentally proven

Therapeutic Touch

Therapeutic (or Healing) Touch (TT) is an energy medicine intervention developed in the early 1970s by Deloris Krieger, a professor of nursing and Dora Kunz, a psychic and natural healer. TT posits that the body, mind, and emotions form a complex Human Energy Field (HEF) and that illness represents a disruption in this. TT practitioners claim to be able to sense this HEF, which extends several inches beyond the skin. The practitioner starts by "centering" or focusing themselves mentally, then assesses the patient by examining the patient's HEF using "the hands as sensors." They then can intervene using a series of hand "movements" to facilitate the symmetric flow of energy through the HEF in a process called "unruffling" and rebalance the field by transferring energy with in the field and by giving the patient some of the provider's own energy [36].

TT practitioners report treating a wide variety of conditions from pain, fever, and decubiti up to improving hemiplegia due to a stroke [37] and saving newborns who have failed conventional resuscitation [38]. Published studies of TT have focused almost exclusively on subjective symptoms such as pain, fatigue, and quality of life but results are mixed, generally showing little effect when compared to sham controls [39]. Studies on wound healing [40] and radiation dermatitis [41] have found no effect. Significantly, studies have shown that TT practitioners have been unable to sense HEFs when tested under controlled conditions [42]. While complications of TT are probably minimal, considerations should be given to unnecessary patient exposure (e.g., in the recent COVID-19 epidemic), delay of definitive therapies and distraction of the provider from other duties [43].

Reiki

Reiki was developed in the early twentieth century by Mikao Usui, a Buddhist spiritualist. The therapeutic aspects of this practice were emphasized by his students and their successors resulting in the healing practice used today. Reiki is felt to affect the vibrations arising from nondual primordial chi, or Tao, as distinguished from the bioenergetic level of chi stimulated by therapeutic acupuncture, allowing the practitioner to rebalance this energy field, removing the causes of illness and restoring overall resilience. Hands-on Reiki treatment involves light touch on a fully clothed recipient who is seated or reclining. If touch is contraindicated, Reiki may be performed with the hands several inches off the body and advanced practitioners are felt to be able to perform Reiki from a distance. A typical treatment involves placing the hands on 12 positions on the head and torso. A typical session lasts 45–75 minutes but may be shorter or longer. The patient need not be conscious [44]. In the USA, there is no central authority regulating the training or practice of Reiki

Reiki treatments are generally directed toward reducing stress, enhancing mood and quality of life, and improving pain. It is recommended for patients with a wide variety of conditions, from diabetics to cancer patients, but is generally felt to help with these previously mentioned areas rather than function as a direct treatment of the medical

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condition. Although studies frequently show improvement in these areas compared to no treatment, there is very little evidence of Reiki causing more improvement than sham Reiki treatments. This implies that these effects may come primarily from the use of a soothing treatment and the attention of a caring professional.

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Patient-Centered Medical Home

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Definition of the Medical Home

The Patient-Centered Medical Home (PCMH) has various titles including, but not limited to, "medical home model," "medical home," "person-centered medical home," and "health home" [1]. For simplicity, PCMH will be used and understood to represent all titles throughout this chapter.

A Patient-Centered Medical Home is not a physical location but a theoretical home whose objective is to integrate various aspects of patient care by utilizing a diverse set of healthcare professionals with a range of expertise. The objective is to develop an individualized model that provides quality, comprehensive, efficient, and effective care [2].

There is no single definition for a PCMH. Various states have developed their own definition as it pertains to their unique patient population [1]. A PCMH should incorporate certain core fundamentals including access, continuity, planned care, population health, care management, patient and caregiver engagement, comprehensiveness, and coordination [3]. The primary

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care collaborative, endorsed by AAFP, does, however, offer a specific definition:

PCMH includes the identification of a personal physician in the context of a physician-directed medical practice, enhanced access to coordinated and/or integrated medical care with a whole person orientation, high standards of quality and safety, and payment that appropriately recognizes the added value provided to patients within the model [4].

History of the Medical Home

The PCMH is not a new design; however, it has gained a renewed sense of popularity in the past decade. The concept was first described by the AAP and later adopted and revised by numerous colleges and academies. Below is an outline of the history of the medical home.

- 1967: The American Academy of Pediatrics (AAP) introduces the concept of a medical home as a centralized location for children's medical records with a focus on patients with specialized healthcare needs [5].
- 1978: The Declaration of Alma-Alta calls for urgent development and implementation of primary healthcare both nationally and internationally – the first international announcement of the necessity of primary care for the health of all people [6].
- 1996: The Institute of Medicine (IOM) defines primary as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health needs, developing a sustained partnership with patients, and practicing in the context of family and community" [7].
- 2001: The IOM recognizes that patients and families are at the center of the medical team and should be partners in making medical decisions by defining "patient-centered care" as "health care that establishes a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and support they require to make decisions and participate in their own care" [8].
- 2002: As a solution to the fragmented US healthcare system, the Future of Family Medicine (FFM) project was initiated which emphasized the need for all patients to establish a medical home and create a model for compensation that sustains primary care [9].
- 2005: Dr. Barbara Starfield describes six primary care mechanisms that benefit health in the article "Contribution of primary care to health systems and health": (1) greater access to needed services, (2) better quality of care, (3) a greater focus on prevention, (4) early management of health problems, (5) the cumulative effect of the main primary care delivery characteristics, and (6) the role of primary care in reducing unnecessary and potentially harmful specialist care [10].
- 2007: The American Academy of Family Physicians, the American College of Physicians, the American Osteopathic Association, and the AAP published "The Joint Principles of the Patient-Centered Medical Home" to create a standardization of the PCMH [11].
- 2010: President Barack Obama signs the Patient Protection and Affordable Care Act which highlights the application and promotion of the medical home model for patients of all ages [12].
- 2011: The Center for Medicare & Medicaid services (CMS) began programs to test changes in primary care delivery and payment [13].
- 2013: State Innovation Models Initiative via CMS promoted state-led delivery transformations to improve quality of care and lower costs, with a majority of focus on primary care [13].
- 2015: The Medicare Access and CHIP Reauthorization Act (MACRA) streamlined multiple quality programs under a new Merit-Based Incentive Payment System (MIPS) [14].
- 2019: After much planning, CMS implemented the first MIPS performance period in 2019. MIPS contain improvement activities similar to the function of Patient-Centered Medical Home model [15].

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Principles and Characteristics of Medical Homes

PCMH can be described as three different conceptual categories: characteristics of primary care practices, patterns of care that patients experience, and interventions applied to primary care practices [16]. "PCMH characteristics" describe how close a practice might be (with greater or lesser degree of success) to the ideal of our PCMH model. "PCMH patterns of care" describe patient experiences such as health outcomes or resource utilization. "PCMH interventions" are empirically testable approaches to improve "characteristics" and "patterns of care" and can be used to inform policy decisions.

The "PCMH characteristics" have been described in various ways throughout its history. In 2007 the American Academy of Family Physicians, the American College of Physicians (AAP), the American Osteopathic Association (AOA), and the AAP published "The Joint Principles of the Patient-Centered Medical Home" outlining essential elements of the PCMH as evidenced by the following [11].

Principles

Personal physician – Each patient has an ongoing relationship with a personal physician trained to provide first-contact, continuous, and comprehensive care.

Physician-directed medical practice – The personal physician leads a team of individuals at the practice level who collectively take responsibility for the ongoing care of patients.

Whole person orientation – The personal physician is responsible for providing for all the patient's healthcare needs or taking responsibility for appropriately arranging care with other qualified professionals. This includes care for all stages of life: acute care, chronic care, preventive services, and end-of-life care.

Care is coordinated and/or integrated across all elements of the complex healthcare system (e.g., subspecialty care, hospitals, home health agencies, nursing homes) and the patient's community (e.g., family, public, and private community-based services). Care is facilitated by registries, information technology, health information exchange, and other means to assure that patients get the indicated care when and where they need and want it in a culturally and linguistically appropriate manner.

Quality and safety are hallmarks of the medical home:

- Practices advocate for their patients to support the attainment of optimal, patient-centered outcomes that are defined by a care planning process driven by a compassionate, robust partnership between physicians, patients, and the patient's family.
- Evidence-based medicine and clinical decision support tools guide decision-making.
- Physicians in the practice accept accountability for continuous quality improvement through voluntary engagement in performance measurement and improvement.
- Patients actively participate in decision-making, and feedback is sought to ensure patients' expectations are being met.
- Information technology is utilized appropriately to support optimal patient care, performance measurement, patient education, and enhanced communication.
- Practices go through a voluntary recognition process by an appropriate nongovernmental entity to demonstrate that they have the capabilities to provide patient-centered services consistent with the medical home model.
- Patients and families participate in quality improvement activities at the practice level.

Enhanced access to care is available through systems such as open scheduling, expanded hours and new options for communication between patients, their personal physician, and practice staff.

Payment appropriately recognizes the added value provided to patients who have a Patient-Centered Medical Home. The payment structure should be based on the following framework:

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- It should reflect the value of physician and nonphysician staff patient-centered care management work that falls outside of the face-to-face visit.
- It should pay for services associated with coordination of care both within a given practice and between consultants, ancillary providers, and community resources.
- It should support adoption and use of health information technology for quality improvement.
- It should support provision of enhanced communication access such as secure e-mail and telephone consultation.
- It should recognize the value of physician work associated with remote monitoring of clinical data using technology.
- It should allow for separate fee-for-service payments for face-to-face visits. (Payments for care management services that fall outside of the face-to-face visit, as described above, should not result in a reduction in the payments for face-to-face visits.)
- It should recognize case mix differences in the patient population being treated within the practice.

In summary, the Agency for Healthcare Research and Quality explains the five functions and attributes of a PCMH as a model of the organization of primary care [17].

- Provides comprehensive care that is accountable for meeting the *majority* of healthcare needs including prevention and wellness, acute care, and chronic care with a team of providers that includes physicians, advanced practice nurses, physician assistants, nurses, pharmacists, nutritionists, social workers, educators, and care coordinators.
- *Provides* patient-centered care that is *cultivated* through partnering with patients and their families and respecting each patient's unique needs, culture, values, and preferences.
- Supports patients in coordinating care across all elements of the broader healthcare system, including specialty care, hospitals, home health care, and community services and supports – particularly critical during transitions between sites of care.
- Delivers accessible services with shorter waiting times for urgent needs, enhanced in-person hours, around-the-clock telephone or electronic access to a member of the care team, and alternative methods of communication such as e-mail and telephone care.
- Is committed to using evidence-based medicine and clinical decision support tools to guide shared decision-making with patients and families, engaging in performance measurement and improvement, measuring and responding to patient experiences and patient satisfaction, and practicing population health management. Sharing robust quality and safety data and improvement activities publicly is also an important marker of a system-level commitment to quality [17].

The Role of Family Medicine in the Medical Home

The "PCMH characteristics" and goals are largely consistent with the skillset of the family medicine physicians. Family physicians are comprehensively trained in screening/prevention, pediatrics, women's health, obstetrics, geriatrics, and behavioral health. Family medicine is a key team leader for the design and implementation of PCMH models.

Studies have shown that the presence of primary care physicians reduces mortality, has better health outcomes and lower costs, and is more impactful than specialists for all-cause mortality. These themes are recurrent when discussing the PCMH. For every dollar put into primary care, the healthcare system saves $13 [18].

The training and goals of the family medicine physician also places them in a position to represent their community to local government as an advocate for improved health policies. Local policies impact how PCMH are able to operate and best impact their community. It will also serve to address barriers to PCMH implementation which include low resources and inadequate staffing or ancillary support.

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Role of the PCMH in the Health System

The PCMH model is being implemented all throughout the country. The goals of the PCMH align well, if not seamlessly, with many healthcare organizations including Centers for Medicare & Medicaid which serve a large portion of our society.

In an ideal PCMH model, patients have improved access, and this tends to be especially important in vulnerable populations. It also avoids duplication of services, helps avoid unnecessary and costly services, reduces medical errors, and keeps patients engaged in their medical care.

A further expansion of the ideal PCMH model includes that of the "medical neighborhood." This concept expands the PCMH model to include all forms of ambulatory care, diagnostic services, pharmacy, and acute and post-acute care facilities. Even more, it further enlists the community and social services available to the population that it serves. The medical neighborhood would serve as another mechanism for improving outcomes, safety, and patient experience, lowering costs, and decreasing medical errors. Medical homes that exist within this structure become critical points of contact and coordination of services to aid patients as they navigate this growing network.

Results and Evidence

The Patient-Centered Medical Home model has been widely implemented in many different patient populations over the last two decades. The cumulative available data offers a mixed picture that suggests a broad failure to deliver large transformative changes, but smaller successes in specific patient populations and disease processes. The confusing state of the PCMH literature underlies the importance of carefully reviewing the methodology of each paper and subdividing based on differences between studying "characteristics" vs "interventions" [19].

Discussing evidence for PCMH should start with studies on "PCMH characteristics." Research findings have shown that healthcare systems with greater "PCMH characteristics" tend to have a more positive impact on utilization, costs, quality of patient care, patient satisfaction, and patient access. For example, a large VA study looked at a pool of 1,650,976 patients who were seen at their PCMH clinics and found that they had fewer ED visits [20]. Another study showed that patients with diabetes who received care from a practice with more PCMH characteristics had 19% greater odds of having well-controlled HbA1c values [21]. The same study also found African Americans had less benefit from efforts to improve blood pressure and HbA1C control, suggesting a persistence in social disparities that needs to consider community factors when implementing PCMH [21].

Unfortunately, despite the positive association between "PCMH characteristics" and healthcare outcomes, the studies on "PCMH interventions" have been much less successful. A prospective cohort study in 2016 with 438 primary care providers and 136,480 patients compared PCMH to non-PCMH practices over a 5-year period. Overall, they found patterns of quality were similar across groups, with some modest changes in utilization [22]. The Maryland Multipayor Patient-centered Medical Home Program which involved 52 PCMH practices had mixed results, with lower costs among Medicaid beneficiaries, but no sustained lower costs in privately insured beneficiaries, no change in provider or patient satisfaction, and higher administrative burden [23]. The strongest null evidence comes from an RCT on healthcare hotspotting. This study on 800 hospitalized patients with very high use of healthcare services found 6-month interventions with intensive case management and coordination of outpatient care did not reduce emergency or hospital utilization. The study questions one key hypothesis of the PCMH model (practice changes can reduce healthcare utilization and costs) and suggests that if PCMH interventions are to be successful, they may require monitoring over a long period of time and with greater community involvement [24].

Overall, the accumulation of disappointing or modest findings highlight the difficulty of implementing PCMH. Practices with greater success at transformation may require support over

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years to complete necessary structural and cultural changes. Providing team and non-visit-based care is also difficult in fee-for-service models, and at least one study has suggested it may require a shift in reimbursement practices to higher levels of capitation payments [25].

Certification, Recognition, and Accreditation

Since its release in 2007, the Patient-Centered Medical Home has provided primary care practices a model to improve the quality, efficiency, and effectiveness of patient care by redesigning their practice. In order to streamline this process, several entities began offering medical home recognition or accreditation for Patient-Centered Medical Homes. The AAFP, AAP, ACP, and AOA developed the "Guidelines for Patient-centered Medical Home Recognition and Accreditation Programs" [23] to help create a standard for accreditation. These guidelines specify that accreditation programs should:

- Incorporate the Joint Principles of the Patient-Centered Medical Home
- Address the complete scope of primary care services
- Ensure the incorporation of patient- and family-centered care emphasizing engagement of patients and their caregivers
- Engage multiple stakeholders in the development and implementation of the program
- Align standards, elements, characteristics, and/or measures with meaningful use requirements
- Identify essential standards, elements, and characteristics
- Address the core concept of continuous improvement that is central to the PCMH model
- Allow for innovative ideas
- Care coordination within the medical neighborhood
- Clearly identify PCMH recognition or accreditation requirements for training programs
- Ensure transparency in program structure and scoring
- Apply reasonable documentation/data collection requirements
- Conduct evaluations of the program's effectiveness and implement improvements over time

Currently, there are four individual certifying agencies that exist and comply with the "Guidelines for Patient-Centered Medical Home Recognition and Accreditation Programs." The agencies include the National Committee for Quality Assurance (NCQA), URAC, the joint commission, and Accreditation Association for Ambulatory Health Care (AAAHC).

Although formal accreditation is not always required to be considered a Patient-Centered Medical Home, some circumstances may require completion of an accredited or recognized program. This is an important factor to keep in mind when establishing an agreement between a practice and another entity like a federal grant, major practice payer agreements, etc.

In Context

The concept of the medical home was first introduced by the American Academy of Pediatrics in 1967 to refer to a central location for archiving a child's medical record. The AAFP and AACP have since developed their own models for improving patient care called the "Patient-Centered Medical Home." The medical home's focus is the patient, and it is important not to lose sight of this among all the metrics. The most important aspect of primary care is the patient-physician relationship. It is important to keep in mind that, while the medical home is valued for its focus on this aspect, physicians should remind themselves of the importance of keeping that concept at the forefront of their minds.

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Chronology: The Evolution of Family Practice as a Specialty in the United States

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Robert B. Taylor and Paul M. Paulman

Year	Event	Significance
1900	At least 80% of American physicians were general practitioners: one general practitioner for every 600 persons	General practice was the predominant model of medical care
1910	Publication of the *Flexner Report* by the Carnegie Foundation, with cooperation of the American Medical Association (AMA)	Prompted changes in methods and quality of medical education: premedical education, biomedical research, and postgraduate training
1940	General practitioners (GPs) comprised 76% of private physicians:	Decline of generalism paralleled the rise of specialty practice
	1950–62% of physicians were general practitioners	
	1960–45% of physicians were general practitioners	
	1970–21% of physicians were general practitioners	
1941	General Practice Certifying Board proposed in AMA House of Delegates	First call for a certifying board for general practitioners; not passed
1946	Section on General Practice of the AMA organized	An early organization of general practitioners with nationwide representation
1947	American Academy of General Practice (AAGP) founded by a small group (no more than 150) of general practitioners meeting in Atlantic City, New Jersey	First major medical organization to require continuing medical education as a condition of membership
1950	First residency training programs in general practice established	Signified need for postgraduate generalist training beyond the internship year
	Publication of journal *GP*	First scientific journal for GPs
1958	Family Health Foundation of America incorporated	Early funding for conferences on generalist education
1960	American Board of General Practice formed	First successful effort to obtain general practice board status

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Year	Event	Significance
1964	19% of US medical graduates entered general practice	Continued decline in numbers of general practitioners
	American Board of Family Practice Advisory Group formed	Developed objectives for the American Board of Family Practice (see 1969)
1965	National Family Health Conference sponsored by Family Health Foundation of America	Studied unmet needs of Americans for comprehensive health care, what practitioner can meet this need, and how he or she can best be trained
1966	Report of Citizens' Commission on Graduate Medical Education: *The Graduate Education* of *Physicians* (Millis Commission Report)	Identified fragmentation in health care and proposed concept of a "primary physician"
	Report of the Ad Hoc Committee on Education for Family Practice of the Council on Medical Education: *Meeting the Challenge* of *Family Practice* (Willard Commission Report)	Recommended training of a "family physician"
1967	Formation of Society of Teachers of Family Medicine (STFM)	First organization of family medicine educators
1969	STFM published *Family Medicine Times* (*FMT*)	First publication (newsletter) for family medicine educators
	American Board of Family Practice (ABFP) founded	Organized as official certifying board for the new specialty
	Recognition of family practice as a specialty on February 6, 1969, based upon approval of the Liaison Committee for specialty boards	The 20th American medical specialty
	Fifteen approved family practice residencies in the USA	Model graduate training programs established
1970	First examination by ABFP	Successful candidates sitting for 1970 and 1971 examinations became Charter Diplomates
1971	American Academy of General Practice changed its name to American Academy of Family Physicians (AAFP)	The academy recognized shift in emphasis to family practice
1972	AAFP fellowships first awarded	Recognized "interest and participation in special educational programs designed to enhance professional competence and the quality of health care provided to the people of America"
	First meeting of North American Primary Care Research Group (NAPCRG)	Forum for presentation of family practice research results
	WONCA (World Organization of Family Doctors) formed	Worldwide organization begins with member organizations in 18 countries
1973	Publication of *Family Practice* (Conn, Rakel, Johnson, editors)	First major family practice textbook
	First National Conference of Family Practice Residents and Student Members	First national meeting of family practice trainees
1974	*Journal* of *Family Practice* began publication	First family practice peer-reviewed journal
	Medical students and residents gain seats in AAFP Congress of Delegates	First major specialty to recognize medical student and resident delegates
1975	Residency Assistance Program (RAP) initiated	Family medicine educators develop guidelines and offer consultation to family practice residency training programs
	STFM Foundation formed	The charitable arm of STFM established
1976	First recertification examination by ABFP	First recertification examination by any medical specialty
	Publication of the Virginia Study in the Journal of Family Practice	First major report of doctor-patient contacts in family practice

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Year	Event	Significance
1977	Doctors Ought to Care (DOC) founded	Championed positive health strategies for the clinic, classroom, and community
1978	Publication of *Family Medicine: Principles and Practice,* 1st edition (Taylor, editor; Buckingham, Donatelle, Jacott, Rosen, associate editors)	First edition of the second major family practice textbook
	Practice eligible route to ABFP certification expired	Candidates for the ABFP certification examination subsequently must have satisfactorily completed a 3-year approved family practice residency
	Association of Departments of Family Medicine (ADFM) established	First organization of family medicine academic units
1979	End of first decade as a specialty: Residency training programs: 364. FP residents in training: 6531. Members of AAFP: 43,956 Diplomates of ABFP: 22,246	Continuing growth of the specialty
	Family Medicine Teacher established	Official journal of STFM
1980	Graduate Medical Education National Advisory Committee (GMENAC) report published	"Near balance" of general practitioners/ family physicians vs. need was predicted for 1990; no change recommended for family practice residencies
1981	*Family Medicine Teacher* became *Family Medicine*	Society's publication becomes an academic peer-reviewed journal
	Family Practice Research Journal began publication	Third peer-reviewed journal in family practice
1982	Report of the Study Group on Family Medicine Research: *Meeting the Challenge* of *Research in Family Medicine*	Documented past achievements and current status; indicated future directions in family medicine research

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Year	Event	Significance
1983	Publication of *Family Medicine: Principles and Practice,* 2nd edition (Taylor, editor; Buckingham, Donatelle, Jacott, Rosen, associate editors)	Principles and practice of discipline integrated as "Family Medicine Content"
1984	Conjoint meeting of STFM and NAPCRG	First joint assembly of family medicine educators and researchers
	Keystone I Conference held at Keystone, Colorado	A time for family practice leaders to meditate and reflect
1985	Liaison Committee on Medical Education (LCME) report *Functions and Structure of* a *Medical School* called for predoctoral training "necessary to enter graduate medical education programs in family medicine. . ."	Official recognition of need for medical schools to present family medicine knowledge, skills, attitudes, and behaviors
	FM student interest groups established at US medical schools	Emphasis on recruitment of medical students to careers in family practice
1986	Family Practice redefined by AAFP and ABFP	New definition affirms independence from other specialties
	More than 20,000 physicians were graduates of 3-year family practice residencies	Record number of residency-trained family physicians
	"Michigan lawsuit" won in United States Supreme Court after 10-year battle	Successful challenge of a Medicare statute that discriminated against family physicians on basis of different fees for the same procedure
1987	First Leadership Skills Development Conference held by the AAFP	Emphasis on enhancing the skills of family physician leaders
1988	*Journal of the American Board of Family Practice* began publication	Fourth US peer-reviewed journal in the specialty
	More than half of all AAFP members were	Most general practitioners had

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Year	Event	Significance
	certified by ABFP (26,500 ABFP diplomates)	become board-certified family physicians
	Keystone II Conference held in Keystone, Colorado	FP leaders meet to reflect and plan for the future
	First examination for Certificate of Added Qualifications (CAQ) in Geriatric Medicine	Joint venture of American Board of Family Practice and American Board of Internal Medicine
	Publication of *Family Medicine: Principles and Practice,* 3rd edition. (Taylor, editor; Buckingham, Donatelle, Johnson, Scherger, associate editors)	Core problems and procedures in family medicine identified
1989	Anniversary of 20 years as a specialty: 384 residency training programs. 7,392 FP residents in training	Family medicine entered third decade as residency-trained physicians began to assume leadership roles
	New active members of AAFP required to be residency-trained family physicians	Affirmed the distinction between family physicians vs. general practitioners and others
	Association of Family Practice Residency Directors (AFPRD) formed	First organization of directors of family practice residency programs
1990	President George Bush signed into law Medicare Physician Payment Reform based on Resource-Based Relative Value Scale (RBRVS)	Projected Medicare payment to be based on resource costs integral to providing a service
	AMA adopted policy that every US medical school should have a family practice department	Recognition of need for medical student exposure to family medicine content and family physician role models
1991	AMA resolved "to develop recommendations for adequate reimbursement of primary care physicians, improved recruitment of medical school graduates, and training a sufficient number of primary care physicians to meet projected national needs"	Evidence of AMA support of family practice and primary care
1992	Medicare physician payment reform began	Beginning phase-in of Medicare fee schedule, eliminating specialty differentials
	Council on Graduate Medical Education (COGME) recommended that half of all medical school graduates enter primary care careers	Recognition that medical schools must meet health care needs of the nation
	Archives of Family Practice began publication	American Medical Association affirmed value of family medicine research through support of a new specialty journal
1993	First examination for CAQ in Sports Medicine for primary care physicians	Joint venture of the American Boards of Family Practice, Emergency Medicine, Internal Medicine, and Pediatrics
	Liaison Committee on Medical Education document, *Functions and Structure of* a *Medical School,* changed to read: "Clinical education programs involving patients should include disciplines such as family medicine, internal medicine, obstetrics and gynecology, pediatrics, psychiatry, and surgery"	Family medicine achieved parity with other specialties in requirements for the medical school curriculum
	Number of family practice residencies exceeded 400	New residencies included inner city, rural, and health maintenance organizations
1994	Publication of *Family Medicine: Principles and Practice,* 4th edition (Taylor,	Emphasis on core problems in clinical family medicine

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Year	Event	Significance
	editor; David, Johnson, Phillips, Scherger, associate editors)	
	End of practice pathway to CAQ in Geriatric Medicine	Candidates must complete formal accredited geriatric fellowship program
1995	American Boards of Family Practice and Internal Medicine called for educational resource sharing and collaborative training	Indicated trend for family physicians to teach our knowledge and skills to other specialists
1996	Publication of *Fundamentals of Family Medicine* (Taylor, editor; David, Johnson, Phillips, Scherger, associate editors)	First predoctoral clerkship textbook based on health problems of a single extended family
	Alaska's first graduate medical education program was a family practice residency	Family practice became the first specialty to have residency programs established in all 50 states
1997	Fiftieth anniversary of the AAGP/AAFP	Fifty years since 1947 founding of AAGP in Kansas City Missouri
	Revised Program Requirements for Residency Education in Family Practice	Changes reflect the evolution of the discipline by no longer defining training elements as derivatives of other specialties and emphasizing the role of family physicians as teachers
	Graduates of US family practice residency programs top 50,000	AAFP annual survey confirms that 50,002 physicians have graduated from FP residencies since the 1960s
1998	Publication of *Family Medicine: Principles and Practice,* 5th edition (Taylor, editor; David, Johnson, Phillips, Scherger, associate editors)	Expanded emphasis on clinical problems in generalist health care
	AAFP Research Initiative begun	AAFP commits $7.7 million to support family practice research
	Center for Policy Studies in Family Practice and Primary Care begun in Washington, DC	AAFP initiative intended to bring a family practice and primary care perspective to national health policy deliberations
1999	Anniversary of 30 years as a specialty: Residency training programs: 474 FP residents in training: 10,632 Graduates of FP residency programs: 56,859	Family medicine continues to prosper as it enters the new millennium
	AAFP begins national practice-based network for primary care research	The network's mission will be to "conduct, support, promote, and advocate primary care research in practice-based settings that (1) addresses questions of importance to the discipline of family medicine and (2) improves the health care delivery to and health status of patients, their families, and communities"
	Practice pathway to CAQ in Sports Medicine ends	One-year sports medicine fellowship required for eligibility
2000	112 departments of family medicine in US medical schools	Continued success of family practice at the beginning of the new millennium
	476 US family practice residency programs	
	61,000 board-certified family physicians	
	Keystone III Conference held in Colorado Springs, Colorado	A forum for family physicians to share ideas and advance the specialty
2001	Certificate of Added Qualifications in Adolescent Medicine begun	Collaborative effort of ABFP, the American Board of Pediatrics, and the American

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Year	Event	Significance
		Board of Internal Medicine
2002	Thirtieth anniversary of the founding of WONCA, which comprises 58 member organizations in 53 countries	World organization of family doctors has total membership exceeding 150,000 general practitioners/ family physicians
2003	*Annals* of *Family Medicine* begins publication	New research journal cosponsored by the AAFP, ABFP, AFPRD, NAPCRG, ADFM, and STFM
	Publication of *Family Medicine: Principles and Practice,* 6th edition (Taylor, editor; David, Fields, Phillips, Scherger, associate editors)	Emphasis on evidence-based health care and patient/ community-centered practice in the new millennium
2004	AAFP-WONCA combined meeting in Orlando, Florida, USA	Largest meeting in the history of family and general physicians worldwide
2005	American Board of Family Practice changes its name to the American Board of Family Medicine (ABFM)	A new name for the specialty, and the *family practitioner* became the family *physician*
2006	*Preparing the Personal Physician for Practice (P4)* project developed	Fourteen family medicine residency programs to put training innovations into practice
2007	Joint Principles of the Patient-Centered Medical Home developed and endorsed by the major primary care physician associations	A health care setting that facilitates partnerships between individual patients and their personal physicians, and when appropriate, the patient's family
2008	The World Health Organization (WHO) publishes *The World Health Report 2008*	Report titled *Primary Health Care: Now More Than Ever* calls for renewal of primary health care as a response to the issues created by globalization
2009	Family medicine celebrates its 40th anniversary as a specialty	Four decades since the specialty was created in 1969
2010	The Patient Protection and Affordable Care Act, commonly called the Affordable Care Act (ACA), signed into law	Most comprehensive overhaul of the United States health care system since the passage of Medicare and Medicaid in 1965
2011	Family medicine residencies achieve a record 94% enrollment rate and add 100 new positions to accommodate the applicant demand	Health system changes seen spurring the increased student interest in family medicine as a career
2012	WONCA celebrates its 40th anniversary	Originally founded in 1972 by member organizations in 18 countries, WONCA grows to 97 member organizations in 79 countries, with a total membership in the member organizations of over 200,000 general practitioners/family physicians
2013	ABFM sponsors pilot of program of 4-year residency training programs	New programs to allow more flexibility in family medicine residency training curriculum
	Family Medicine Working Party launches the *Family Medicine for America's Health* initiative	Multiyear strategic program to define the role of the 21st century family physician
2014	AAFP report *Family Physician Workforce Reform* calls for 65 new family medicine training positions yearly over the next 10 years	Proposal calls for adding 4,475 family medicine training positions by 2025, projected to end the shortage of family physicians in the United States
2015	AAFP Foundation begins the Family Medicine Leads Program and sponsors the First Emerging Leader Institute for medical students	New medical student program offers tracks in policy and public health leadership, personal and practice leadership, and philanthropy and mission-driven leadership

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Year	Event	Significance
2016	Publication of *Family Medicine: Principles and Practice,* 7th edition (P. Paulman, R. Taylor, editors; L. Nasir, A. Paulman, associate editors)	A new editorial team for the book "by family physicians for family physicians," and the new edition published both in digital and print media
2017	Fiftieth anniversary of the founding of STFM	The STFM mission: Advancing family medicine to improve health through a community of teachers and scholars
2018	Fortieth anniversary of ADFM	The ADFM mission supports academic departments of family medicine to lead and achieve their full potential in care, education, scholarship, and advocacy to promote health and health equity
2019	Fiftieth anniversary of founding of Family Medicine as a specialty	A third generation of leaders for the specialty
2020	Family Medicine Advocacy Summit held in Washington, DC, USA	An opportunity for family physicians to get practical, hands-on experience in advocacy within the legislative process
2022	Publication of the 8th edition of *Family Medicine: Principles and Practice* (editors: P. Paulman, R. Taylor, L. Nasir, A. Paulman	The latest edition of the reference book compiled by family physicians for family physicians. First published in 1976
	Fiftieth anniversary of the founding of NAPCRG	The world's largest organization devoted to research in family medicine, primary care, and related fields

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Engaging the Future of Family Medicine and Healthcare

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Warren P. Newton

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Introduction

In the late fourteenth century, Florence had survived the Black Death and begun its transformation to a center of cloth making, international banking, and the revival of classical learning. Unfortunately, the greatest statesman of the age, the Milanese leader, Giangaleazzo, came to power and began a series of military and political campaigns to take control of what is now northern Italy. By 1402, Florence stood alone with Milan's armies on the boarder and about to invade again. Remarkably, however, the plague spread through the countryside and killed the Milanese leader, lifting the immediate threat to the city. Having survived the most serious crisis of their history, the Florentines explored why they came so close to extinction. Their answer, in part, was their system of education, an arid scholasticism which emphasized the importance of scholars being detached from society. In its place, they put in place a new approach to education, once that put scholars in service to the needs of society. This new approach to education, civic humanism, is now known as the liberal arts [1].

Family Medicine and the US healthcare system face such a challenge today. As a child of the 1960s' demand for access to community physicians, Family Medicine grew to hundreds of residencies in a decade, and family physicians are now the largest and most widely distributed group of personal physicians. Family Physician scope of practice remains the broadest of clinicians, and, in

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many regions, family physicians continue to be critical for access to health care across the continuum of care [2]. At the same time, however, despite the demands of the Affordable Care Act and huge demand in the market, the numbers of students from allopathic medical schools interested in Family Medicine has begun to drop, burnout is widespread, and scope of practice is diminishing.

The broader health care system is similarly coming to a crisis. American healthcare has always been dynamic, with a parade of new drugs and devices, but the amplitude and speed of recent changes have not been seen in two generations: they represent ***transformation***. A major component of the transformation is the rapid consolidation of hospitals and health systems, driven by health care reform, the promise of payment for population health, and market and regulatory forces. In parallel are the rapid spread of integrated electronic health records and employment of physicians. The majority of US physicians are now employed, as are almost 70% of family physicians [3]. A second phase of transformation is just starting. Changes in genomics are revolutionizing cancer and autoimmune disease treatment and promise more. Augmented intelligence promises to change health care as much as has already happened in banking and retail businesses. Attracted by the opportunity for profit, new business models are coming into medicine – CVS and Aetna, Humana and Walmart, Amazon, JP Morgan and Berkshire Hathaway along with many others. And the COVID pandemic will have long term effects on health care, including likely widespread adoption of telehealth and lasting changes in the organization and financing of health care.

Unfortunately, despite transformation of care, and despite health care reform, the population outcomes of health care in the USA are the worst among developed countries, and getting worse. As the National Research Council demonstrated [4], Americans are sicker and die earlier than citizens of comparable countries. This is true at all ages and for almost all diseases – and at a health care cost much greater than comparable countries. As examples, Figs. 1 and 2 depict the

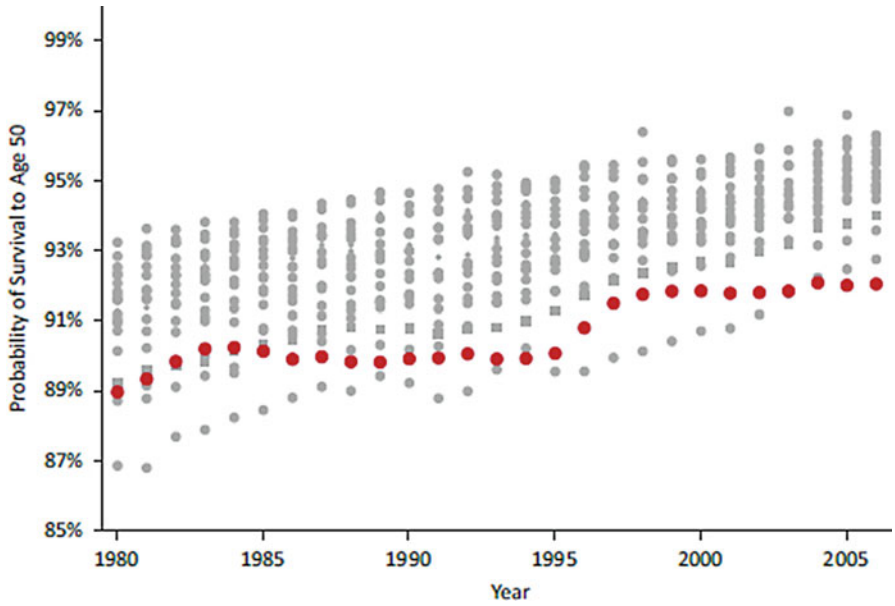


Fig. 1 Probability of survival to age 50 for males in 21 high-income countries, 1980–2006. (Notes: Red circles show the probability of newborn male in the United States will live to age 50. Grey circles show the probability of survival to age 50 in Australia, Austria, Belgium, Canada, Denmark, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the United Kingdom, and West Germany. Source: National Research Council (2011, Figs. 1–5))

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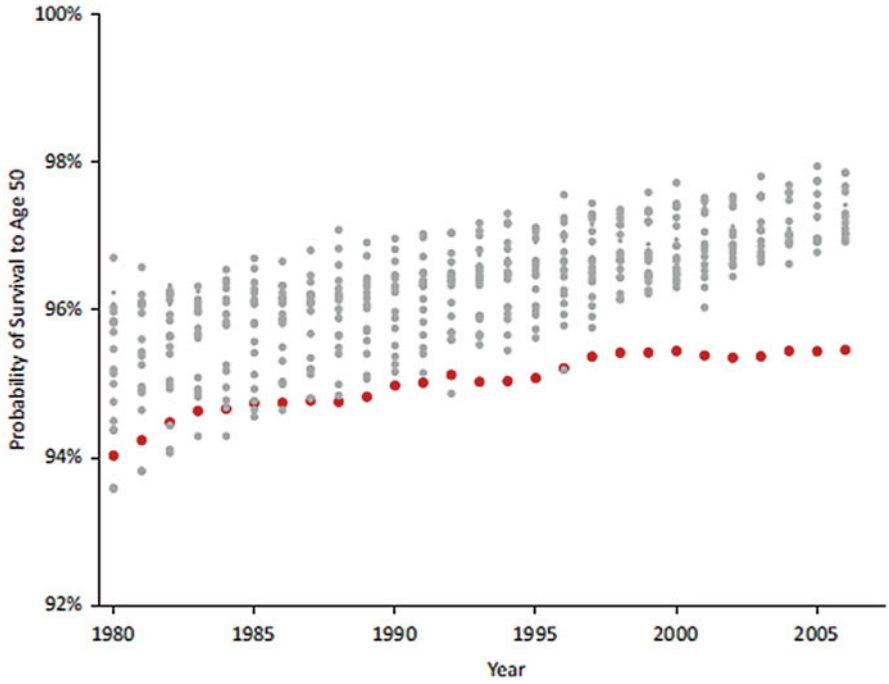


Fig. 2 Probability of survival to age 50 for females in 21 high-income countries, 1980–2006. (Notes: Red circles show the probability a newborn female in the United States will live to age 50. Grey circles show the probability of survival to age 50 in Australia, Austria, Belgium, Canada, Denmark, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the United Kingdom, and West Germany

likelihood of survival beyond the age of 50 [4], and Fig. 3 compares US public and private health care expenditure to other countries [5]. More recently, it has become clear that US life expectancy has begun to decline, as the result of increased mortality from many diseases [6]. This was apparent even before the COVID pandemic highlighted dramatic disparities of incidence and mortality for Blacks, Hispanics, and Native Americans.

The premise of this chapter is that both Family Medicine and the broader health care system are in a phase of dramatic change. Family Physicians, as the most common and widely distributed personal physicians, currently play a major role in health and health care across the country. At the same time, as the needs of society are changing, family medicine must change to meet society's needs and help lead the health care changes necessary to improve health and health care. What follows summarizes the origin and current role of family physicians, the drivers of primary care's population benefits, the challenges health care faces, and how family medicine must evolve to meet the needs of society and the broader healthcare system.

The Origins and Current Role of Family Medicine

In 1960, in a classic article in Lancet [7], Fox argued the health care needed a new kind of doctor, a personal doctor with additional training and support who could address the large majority of a patient's problems and, if necessary, accompany the patient through an ever more complex health care system. Combining the heritage of general practitioners with the sixties' call for access to care, and with impetus from the Folsom, Millard, and Willis reports [8], the new specialty was born with the creation of the American Board of Family

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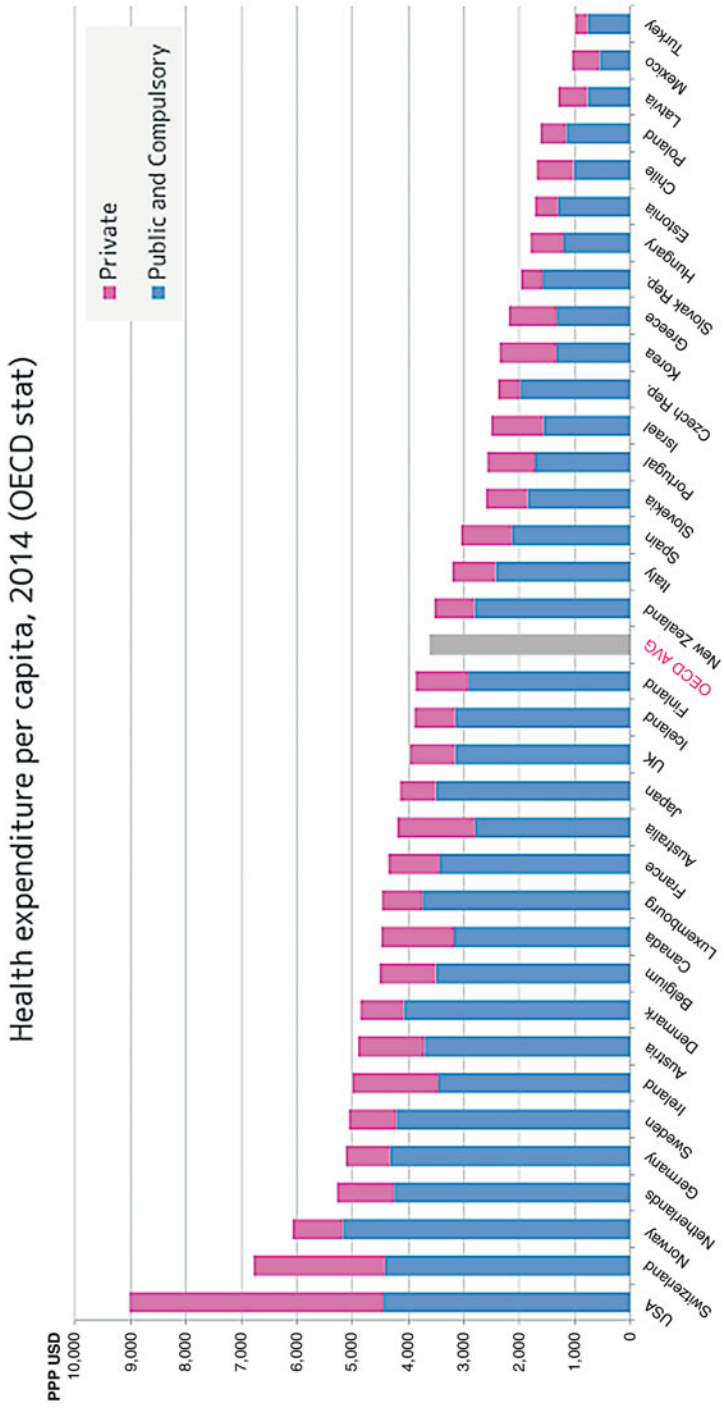


Fig. 3 OECD.Stat: Health Expenditure and Financing. Organisation for Economic Co-Operation and Development

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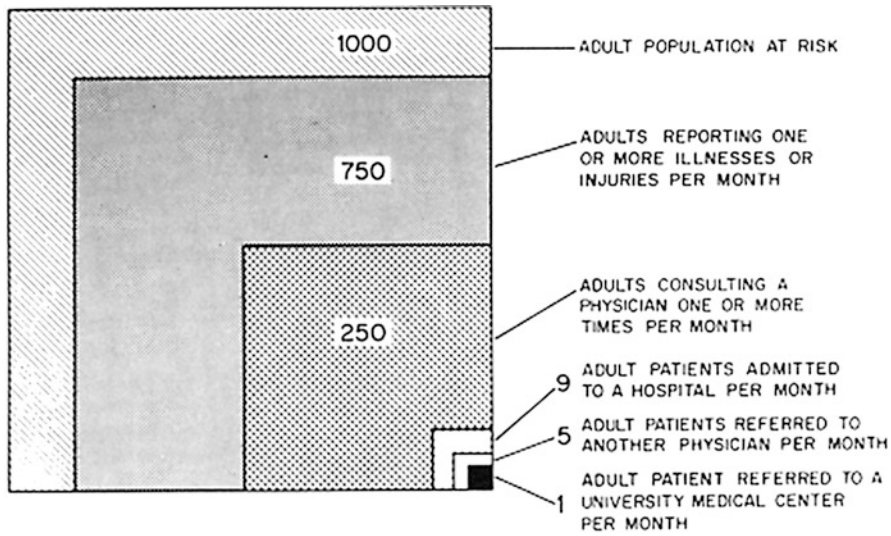


Fig. 4 Ecology of Care. (Monthly prevalence estimates of illness in the community and the roles of physicians, hospitals, and university medical centers in the provision of medical care (adults sixteen years of age and over). White et al. [11])

Medicine in 1969. The new specialty was marked by a commitment to 50 hours of CME a year, the importance of ongoing and independent assessment of cognitive expertise, and the conviction that both knowledge and performance in practice were important. Powered by the social movement of the 1960s, the specialty grew very rapidly, with hundreds of residencies beginning over the next decade.

Family physicians now constitute the largest population of personal physicians in the USA, growing rapidly even as many fewer go into general medicine and general pediatrics [2]. For all common chronic diseases, the large majority of Americans who name a personal physician name a family physician [2, 9]. Family physicians also have a broad scope of care, providing substantial amounts of inpatient care, obstetric care, and emergency room care, especially in rural areas. Maps of the USA without family physicians demonstrate dramatic number of physician shortage areas [10]. Large numbers of nurse practitioners and physicians' assistants are being trained, and many go into primary care, often with family physicians or but many more go into subspecialty practice [2].

It is important to put primary care into the context of the broader health care system. Kerr White in a classic study of the ecology of medical care in 1961 [11] used current evidence to describe what happens to patients are seen in average month. As Fig. 4 depicts, of 1000 adults over a month, 750 will develop symptoms, 250 will go to a primary care doctor, 9 will be hospitalized, and 1 will be hospitalized in an academic medical center. Interestingly, 40 years later, Green demonstrated that the proportions were still approximately the same [12]. The figure demonstrates the major role of primary care in health care as well as the need for medical education outside of academic hospitals.

The Primary Care Advantage

In considering the future of Family Medicine, an important first step is to explore the core functions of primary care. At this stage, there is a deep and broad literature on the impact of primary care. Starting with Starfield's classic article in the Lancet [13], there has been ample demonstration that countries with robust primary care have increased quality of care, decreased cost, and better patient satisfaction. While Starfield and others' work is largely ecologic in nature, the findings have been

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replicated across states and other levels of organization [14].

What about primary care provides such a robust health benefit? The key elements have been termed the "four Cs": first contact, continuity, comprehensiveness, and coordination. First contact care means access to care, along many dimensions including location, hours, cost, and trust. Especially after the COVID pandemic, access does not necessary mean *in person*, but in happening some way for ongoing care and improvement of health. Continuity of care makes possible trusting relationships and the knowledge of patient context that drives trust, medication adherence, behavior change, and shared decision making. Comprehensiveness is taking care of the whole person, supporting prevention and well as diagnosis and treatment and mental as well as physical problems. Comprehensiveness is often operationalized as a clinician being able to care for almost all of the problems that patients coming in have in a given day. Finally, coordination is necessary as patients travel through the health care system and is especially important as they age and have multiple medical problems.

Of course, these core functions are interrelated – for example, continuity of care makes comprehensiveness of care and coordination more feasible. What Starfield and others have demonstrated is that the better these functions are achieved by primary care in a particular country or region, the greater the benefit to the health of the population. It is important to recognize that these are functions, not specific kinds of providers, and that support of primary care through data exchange, connections to communities and public health and robust connections with hospital care is critical. Importantly for the policy discussions, there is little in the literature that says that primary care must be provided by family physicians as opposed to other specialties or professions. In addition, primary care in the USA and Canada is distinguished by its breadth of scope. Family physicians practice not just in continuity of care in the community but also often in the hospital, the labor deck, in nursing homes, and many other community settings.

The Challenges of the Future

The crisis facing health care is complex, including fundamental changes in the clinical problems we are facing, growing complexity of the health care system, continuing increases in the cost of care and an increasing loss of trust in health care systems and in doctors. Clinically, and very different from the time of the founding of family medicine, multimorbidity drives the vast majority of cost, mortality, morbidity, and cost [15]. Health care – and family physicians – must thus be able to address the challenges of patients with many clinical problems. There are also new clinical problems. In addition to the threat of emerging infectious disease made clear by COVID, there has also been epidemic opiate and other substance abuse. Opiates now kill more than automobile accidents. More broadly, deaths due to behavioral problems have grown greatly and suicide attempts among adolescents have increased dramatically [16, 17], while social issues such as isolation, poor health literacy, and lack of access have common and important clinical implications.

Contemporary organization of health care has not kept up with the dramatic changes in disease and in society. The Center for Medicare and Medicaid services has emphasized that poor transitions of care remain a major cause of unnecessary cost and poor quality [18]. To what extent has the growing separation of hospital care from primary care contributed to this problem? Vast "obstetrical deserts [19]" have been created with the accelerating closure of rural hospitals and the lack of family physicians to deliver babies in rural communities. The lack of integration of behavioral health and physical health has greatly increased the cost and dyscoordination of care, even as the COVID pandemic has underscored the importance of a robust link between primary care and public health [20]. Finally, both COVID and the new civil rights movement have again underscored the presence of shameful disparities of health outcomes across race, ethnicity, and socioeconomic status.

Family Medicine faces its own crisis, with decreasing scope of practice and, like other specialties and professions, epidemic burnout. Phillips underscored the risks of the current

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trajectories of Family Medicine. If not addressed, they portend a dystopic future:

> The role of the US family physician is to provide episodic outpatient care in 15-minute blocks with coincidental continuity and a reducing scope of care. The family physicians surrender care coordination of care to care management functions divorced from practices and works in small ill-defined teams whose members have little training and few in depth relationships with the physicians and with patients. The family physician serves as the agent of a larger system whose role is to feed patients to subspecialty services and hospital beds. The family physician is not responsible for patient panel management, community health or collaboration with public health. [21]

On the other hand, by taking advantage of technology and other advances, Phillips paints a different and more positive vision for the future of Family Medicine based on greater use of technology and other advances:

> Family physicians are personal doctors for people of all ages and health conditions. They are a reliable first contact for health concerns and directly address most health care needs. Through enduring partnerships, family physicians help patients prevent, understand, and manage illness, navigate the health system, and set health goals. Family physicians and their staff adapt their care to the unique needs of their patients and communities. They use data to monitor and manage their patient population and use best science to prioritize services most likely to benefit health. They are ideal leaders of health care systems and partners for public health. [21]

The Way Forward for Family Medicine

The first step is to commit to the goal of improving health and healthcare. In 2013, Don Berwick and his colleagues set out for the nation a triple aim – improving health, patient experience and reducing the cost of care [22]. At the same time, as burnout across medicine and other health professions has increased, we have realized that resilience and wellness of health care workers is a necessary foundation for the triple aim. The preventable deaths of health care workers in the COVID pandemic as the result of the lack of personal protective equipment have underscored this issue.

Within this overall goal, what is the special role for family medicine and primary care? Primary care, re-envisioned robustly, and implemented by personal physicians and their teams, can play an important role but it is necessary to reconsider the core functions of primary care and adapt them to the 2020s. Post COVID, both first contact care and continuity of care will likely include telehealth and often team based care; the innovation challenge will be to organize care to support continuity of care, patient engagement, and the shared decision making so critical for managing critical clinical decisions. Although family physician scope of practice has declined in recent years [23], the COVID Pandemic has highlighted the value of flexibility of family physicians to take care of patients across the continuum of care – on the wards, in the ICU, in the diagnostic tent, or by a hybrid in person/telehealth role. Can new models of care with family physicians rotating through both the office and the hospital address the cost and quality problem of transitions of care, while preventing as many hospitalizations as possible? Can family physicians providing more emergency care, prenatal care, and deliveries with caesarian section capability help rural communities survive, helping to reverse recent increases in rural mortality? In an age of multimorbidity, when large proportions of Medicare patients see over 15 doctors a year or are on over 10 medications, can better continuity and comprehensiveness, supplemented by smart care coordination, improve care? Finally, can family physicians working and engaging in communities help improve disparities and increase social capital?

A key priority at the health system and payer level will be developing, testing, and spreading innovations of care that improve population health. Population health has had increasing attention over the last decade but means different things to different people. Population health is more than a killer app or an EHR or just having an integrated clinical system! A major challenge will be combining innovation in delivery models with payment reforms which focus on defined populations and have primary care at their foundation and all both growth and sustainability. Family physicians have played major roles in large scale practice demonstration

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projects; given family physicians' clinical breadth, interpersonal skills, and pragmatism, it is not surprising that there is a growing interest in development of family physicians in leadership roles in large systems [24].

At the individual and community level, family physicians must adjust to being employees in increasingly large health care systems. The large majority of family physicians are now employed, with increasing numbers in large multispecialty practices or clinically integrated systems. Post COVID, it is likely that this trend will accelerate. For a specialty and culture born of small group independent practices, this has major ramifications. Learning how to navigate a large system clinically takes time and practice, as does effective advocacy for both individual patients and system changes. The intrinsic professionalism we bring to our work must be adjusted to the new context.

At the level of clinical care, the most important challenge will be learning to manage panels and populations of patients. Most family physicians are well trained in the care of individual patients but have not been trained in the skills for managing panels. But panels/denominators are fundamental for improving access, effectiveness, and patient experience. Thinking at both the population and the individual level requires both training and practice.

Another key challenge will be adopting new technology thoughtfully. Virtually all of primary care in the USA switched to telehealth in the course of a few weeks in March 2020 – a stunning achievement that demonstrates the professionalism and flexibility of our health care profession. The technology challenge will be much greater than telehealth – it is making sense of the plethora of devices and tests that will allow family physicians to broaden their scope across the continuum of care. It is making cost-effective use of new pharmaceutical agents that cost thousands of dollars a month: it is making genomics useful beyond cancer treatment and autoimmune diseases; it is building AI into patient care systems. American healthcare is awash with technology and data, from new tests to new apps to new drugs and devices: all will sound good, almost all will increase costs, and a few will improve health outcomes. The challenge of thoughtful cost-effective adoption of technology is one of the most important roles of personal physicians.

Where does team-based care fit in? A large proportion of family physician currently practice with NPs (55.9%), PAs (42.5%), Pharmacists (25.8%), and Social Workers (26.3%) but how to work together optimally over time is still evolving [25]. The doctor patient relationship is key to the shared decision making and the behavioral changes necessary to address chronic disease, but it is also clear that much of the care perceived by patients is provided by team members. Our models for team-based care come from the inpatient setting, where patients were in the hospital for a very long time and different professionals work together over weeks. In the primary care setting, however, teams function very differently. A large office can see 300 patients in a day; teams evolve, start, and stop hour by hour. In primary care, moreover, patients are vertical rather than horizontal – to a much greater extent than patients in the hospital, patients can choose to comply or not with recommendations. It is thus critical to involve patients and family in the team of care. Improving team-based care is thus important, but who should be on the team and how to best deploy teams remains one of the most exciting challenges in the specialty.

Addressing these problems will require a new kind of ongoing professional development. In 1947, the American Association of General Practice made a remarkable commitment to lifelong learning through 50 hours a year of continuing medical education (CME) [26]. At the time it was, and still is, a major commitment – by the biggest commitment of any specialty. In the three generations since that commitment, however, there has been a stunning shift in pedagogy. We now understand that active learning is vastly better than the passive learning typical of "butts in the seats" CME, that physicians like other experts are not good at assessing their own knowledge, and that the right kind of assessment drives learning [27]. All of these mean that the continuing professional education system for family physicians must change dramatically.

Perhaps the most challenging task for the family physicians of the future will be maintaining connection with their patients through many

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channels and multiple priorities. The goal remains both care and cure – providing treatment and counsel, improving quality of live, and promoting empowerment through shared decision making, keeping up to date, while balancing the needs of the individual and the population, keeping up to date and engaging in one's own community. Such a complex task requires the most able of physicians and the professionalism to commit to ongoing self-assessment and improvement.

Conclusion

Since its founding as a specialty in 1969, Family Medicine has met the need of society for access to community-based physicians. The specialty has grown to become the largest and most widely distributed group of personal physicians, and family physicians play a huge role delivering care for patients and communities across the country. Now, however, as the progress of health and health care falters, family medicine must evolve to meet the evolving needs of society. Personal physicians can and must contribute to improving health and healthcare, one patient at a time, one community at a time, and one health system at a time. After recognizing the time in history, the first step, the most practical step, is to change our educational systems across the continuum, from undergraduate to graduate to continuing medical education. Like the Florentines did more than 600 years ago, like the AAGP and the ABFP did 50 years ago, we must start with education, in service to society' needs.

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Normal Laboratory Values/Adult Patients

Clinical Chemistry Tests

Alanine aminotransferase (ALT, SGPT)	13–48 U/L
Albumin	3.6–5.2 g/dL
Alkaline phosphatase (ALP)	35–120 U/L
Amylase, serum	44–128 U/L
Aspartate aminotransferase (AST, SGOT)	15–41 U/L
Bilirubin, conjugated	0–0.2 mg/dL
Bilirubin, total	0.2–1.2 mg/dL
Calcium	8.5–10.5 mg/dL
Carbon dioxide (CO_2), total	23–30 mEq/L
Chloride	98–109 mEq/L
Creatine kinase (CK, CPK)	40–260 U/L
Creatinine	0.7–1.2 mg/dL
Gamma glutamyltransferase (GGT)	5–40 U/L
Glucose, fasting	65–110 mg/dL
Hemoglobin A_{1C}	5.0–7.0% of total Hb
Iron, serum	50–170 μg/dL
Iron-binding capacity, total (TIBC)	270–390 μg/dL
Lactate, serum (venous)	5.0–20.0 mg/dL
Lactate dehydrogenase (LDH)	110–260 U/L
Lipase	10–140 U/L
Magnesium	1.5–2.5 mg/dL
Potassium	3.5–5.1 mEq/L
Prostate-specific antigen	0–4 ng/mL
Protein, total	6.1–7.9 g/dL
Sodium	136–147 mEq/L
Troponin I	<2.5 ng/mL
Troponin T	<0.2 ng/mL
Urea nitrogen	6.0–20.0 mg/dL
Uric acid	2.6–7.2 mg/dL

Lipid Panel

Cholesterol, total	160–240 mg/dL
HDL cholesterol	>40 mg/dL
LDL cholesterol	<130 mg/dL
Triglycerides	55–200 mg/dL

Thyroid Function Tests

Thyroid stimulating hormone (TSH)	2–11 μU/mL
Thyroxine, free (FT_4)	0.8–2.4 ng/dL
Thyroxine, total (T_4)	4.0–12.0 μg/dL
Triiodothyronine (T_3)	70–200 ng/dL
Triiodothyronine (T_3) resin uptake (T_3RU)	25–38%

Blood Gases

	Arterial	Venous
Base excess	−3.0 to +3.0 mEq/L	−5.0 to +5.0 mEq/L
Bicarbonate (HCO_3)	18–25 mEq/L	18–25 mEq/L
pO_2	80–95 mm Hg	30–48 mm Hg
O_2 saturation	95–98%	60–85%
pCO_2	34–45 mm Hg	35–52 mm Hg
Total CO_2	23–30 mEq/L	24–31 mEq/L
pH	7.35–7.45	7.32–7.42

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Hematology and Coagulation Tests

White blood cell (WBC) count	4.4–11.0 K/mm^3
Hemoglobin	12.2–15.0 g/dL
Hematocrit	37.0–54.0%
Red blood cell (RBC) count	3.80–5.20 million/mm^3
Mean corpuscular volume (MCV)	85.0–95.0 μm^3
Mean corpuscular hemoglobin (MCH)	26.0–34.0 pg/cell
MCH concentration (MCHC)	32.6–36.0 g/dL
Red cell distribution width (RDW)	11.5–15.0%
Platelet count	150.0–420.0 K/mm^3
Reticulocyte count	0.5–1.5% of RBCs
WBC differential	
Neutrophils	38–70%
Lymphocytes	16–49%
Monocytes	2–9%
Eosinophils	0–5%
Basophils	0–2%
Sedimentation rate	
Adult male	≤15 mm/h
Adult female	≤20 mm/h
Coagulation tests	
Fibrinogen	200–400 mg/dL
Partial thromboplastin time (PTT)	60–85 s
Activated PTT	25–35 s
Prothrombin time (PT)	11–14 s

(continued)

Note: The reference intervals shown are for adults and may vary according to technique or laboratory, or as new methods are introduced. Always consult the reference range for your own laboratory.

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